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Jarrard et al.

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(45) **Date of Patent: Nov. 20, 2018**

(54) **UNBIASED DNA METHYLATION MARKERS DEFINE AN EXTENSIVE FIELD DEFECT IN HISTOLOGICALLY NORMAL PROSTATE TISSUES ASSOCIATED WITH PROSTATE CANCER: NEW BIOMARKERS FOR MEN WITH PROSTATE CANCER**

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(73) Assignee: **Wisconsin Alumni Research Foundation**, Madison, WI (US)

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(21) Appl. No.: **14/226,291**

(22) Filed: **Mar. 26, 2014**

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Related U.S. Application Data

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(51) **Int. Cl.**

C40B 30/04	(2006.01)
C12Q 1/68	(2018.01)
C12Q 1/6886	(2018.01)

(52) **U.S. Cl.**

CPC ***C12Q 1/6886*** (2013.01); *C12Q 2600/154* (2013.01)

(58) **Field of Classification Search**

CPC C12Q 1/6886; C12Q 2600/154

See application file for complete search history.

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International Search Authority, Notification of Transmittal of the International Search Report and the Written Opinion of the International Searching Authority, or the Declaration; International App. No. PCT/US2014/031957, dated Oct. 6, 2014.

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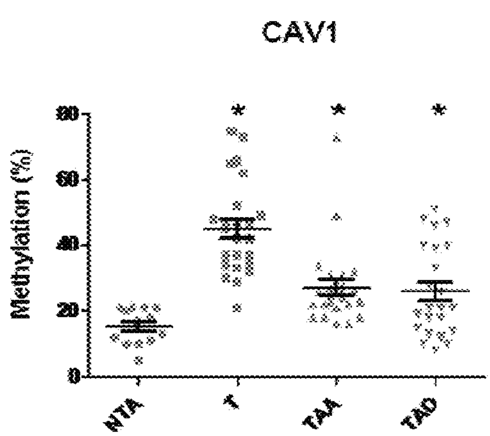
(57) **ABSTRACT**

A method of detecting the presence of a prostate cancer field defect in a human subject comprising the step of (a) obtaining genomic DNA from the human subject and (b) quantitating methylation in at least one target region selected from the group consisting of CAV1, EVX1, MCF2L, FGF1, NCR2 and WNT2 and EXT1 and SPAG4 target, wherein significant methylation changes indicate the presence of prostate cancer or a prostate cancer field defect, wherein the change is relative to tissue from a second human subject who does not have prostate cancer.

12 Claims, 39 Drawing Sheets

Specification includes a Sequence Listing.



CAV1 (caveolin 1, caveolae protein), Chr7

SEQ ID NO:1

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agaagc ctgcggctgc cccctcgccg ccgaggtcct gcgggtcctg cgggtcctgc
gtgctgagcc ggggcgtgcg cgggcggggg ccttcggacc gcgcggcggg gcctgccctg
acccctggcg gcgggcgggg gaggcaggcg cgccctgcag agtacagagg ggtgtggtgt
cctctgcgag atcctcttaa aaagctggct acgcgcaggc ggtttctgtg cacggagccg
tagctgtcgg agcggttagt tcgatttcga gctcgaggtt tcccccgccg ccaggctgac
ttctcatcgc ttgtttttct ttttgcattt ttcctcccac cgccgttgcc gccctccccg
tcctggccgt ccgccctccg ccctctgcag ggacatctct acaccgttcc catccgggaa
cagggcaaca tctacaagcc caacaacaag gccatggcag acgagctgag cgagaagcaa
gtgtacgacg cgcacaccaa ggagatcgac ctggtcaacc gcgaccctaa acacctcaac
gatgacgtgg tcaaggtaag ccaaggcgac caacagggaa gggctgggac agctctcctc
tggcagttag cccgtgcatc cttctttagc attgccgtgt acgcacaccc caccccgccc
cctacacgcg cacacacaca cacacacaga gttttgtggg tttgatgtgt gggagctccc
gcagtcggca gaaacgttac atctcccttc ccccatctcc ccccaatagt tagttcagct
gaaattcagc taaagtgagt tttgtagaag ttcctataac tacactttta tcctagcaaa
tgagcctatt gacctcagca acagacggcc catactcctt gggacggtga gatggttcct
atccattccc aggttgaaag tctagtgaca ggtccccact gcacgtggca ttaagacagt
cagataattg tgtcaggtct tgtgctgagg atgagtcaga atacaagatg ggcatgttcc
cccaactaaa acgatgggaa gtgattttct taaa
```

Fig. 1

EVX1 (even-skipped homeobox 1), Chr7

SEQ ID NO:2

accgtgcccc tccgctcccc gggcctccca ctgcgcccac ccttcacttc ggcgcaggcc

aggaggaaga cactcccttc ccctagggca ggatggctgg ggggacccac ctgagcaact

ctctctgcta tctgcgttct ggcgggggtc tcctactgtg ttctggcatt ggcgggactg

agggtgacag cagtgccttg agtgcggggt gctgaggggg cggatgcaag tcctggactt

gggggattcg aagctcaccc caagcaccca gtgtttcaac tgctcgggga atgcttcaat

tgctcgggga agacactttc cccaggcgag ggcaagatca aacgccgatc cgggcagttt

gtggctggca gggtgtaaga ggcatggagg cgcggaagcc aggagtccat aaaggaccgt

aaaattgcgg cccacttggg cagcccgggt gctgcagccc tccgaccagt ttgcacgtcg

gtcagaggtc caaattacct tgtcacttcc cgggcttcgc ggcgccaggt cggaaatggt

cccaatggtc taattgcctt tggtctccgg ttgcatttga aaaggcagag atcgggtcct

ccccccttcc cctttccttc ctagtcccac ttctccaccc aaaggaaaag gagctgcagg

gggctggagc cccacccttc tcagaggtag gcccaaaggg gggctggttt aactggagaa

cccctcccca ccaaaggcta atgggaaagg ggtggatagc ccggaaggga gtttccctct

gtgccaacaa tcacctcccc agaaggggggt agaaaactgg gcgcgggttg gtggggggga

ggagagggga gcccaccagc agacactcct ccacagaact gtaggagtgg gtggaaagag

cctgggggcg ggggggagaa agaccacccc ctggtcttgg cagccaacgc cttgttgaat

acctgcacct accccttact atcttatcac cgatttcacc cagcctcctt cccataaccc

tcagaacaac ctggactcca ctcacatata

Fig. 2

MCF2L (cell line derived transforming sequence-like), Chr13

SEQ ID NO:3

cc tgaggggtct gttccagggg agccagggct ctccgtgtcc cgacgcggtt
gcctcacccc atgcccctca ggaaatgctg aaatacagca ggaactgcga gggggctgag
gacctgcagg aggcgctgag ctccatcctg ggcatcctga aggccgtgaa cgactccatg
cacctcatcg ctatcaccgg ctatgacgta aggcgcccag atgcccggtc ttccccgccg
cctccgtgga atacaccagc ccagcaactt ggcggcctcc ctgcacacgc ccctcgcttt
ggtgtgaatg tgcaggttct gggcaggagg tctggggtgg tccctagata agcccactcc
caggccccac agccgggtcc acagacccca cagccgggtc cacagacccc actgggctct
ctgggacgtg gagaaaatca ggaagcgtcc cttgcttgga gggcacgcat ctccagcagg
aacgcagctc agacctcctc actccttgtc ttctcctggg gaggaggcgt ggctcggagc
agacgtgact tctgttttct gggctgcgat ttgcaggctg gtgacttaga gcaagtggcc
ccagaaggca gatgtcactt tccccgtaga gccccacatc aggtcacagc ttattcatct
tttgtccgtc tttatgtcca cccagcactc attctcaggt gttttttttt taactaatag
agttgattta ttgcagcaat ttttggtttg tgagataatt gagtataaat cagaggccct
gaggcttccc ctagtgttga catttagcat gggtgccaca cctgccacac atggtgaact
agcgctgatg ctgattagtg actgagggcc gttccccttg gagctcactc tgggtgctgt
gcattctgcg gtttggacag gcgtgtaaca tcctacaccc agcgctagag catcacacag
agcagcttca ctgtcctaga agcccatgtg ccccgccagt ccatccctcc tcccccagcc
cctggcacct gctgacctgt cagtctccac gagcttgc

Fig. 3

FGF1 (fibroblast growth factor 1), Chr5

SEQ ID NO:4

ATAATCGTGAGAAGGAAGCTCATGCTTCTGTCCTCGACTGGCTTGTAGTCTAGTCAAGAAGACTTGAGGGC
TGATGAGCTTTTCAGAGATGGAAATAGAGGATACTGTGCCCCGTGGCCTCTGCTCTGCCCAGCCCCCTACC
AGTAACCAACAATTTTCCAGAAGAATTTCCAAATTCCCTTCTCCAAAGTCTCCACTGGCTCCACTTTCATT
TGCTTGCAGAAAAAAGTCTAAATGCTTTGGAACAGCATCATTCAAGGTCCTCTATGATCTGACTCCAAGCT
AGCTTGCACTAACCCTGTGTGTCCCTGAAAACCCCCCGCTCAGCGGCATCAGCCATGCATGCTGGGCGAAG
ATGCCCTCTACTTGCCCACCCCTGGGCCTCTGTTCAAGTGATTCCTTTATTCCATGCCCACATATGTAAAA
CCTGTTTGTCCTTCCTGCTGAGATGCCACATCTTCCAGAAAGTCCTCCTGACCCCTTCCTCTTCAGCCCTC
CATCCATCCCCCCAGCCCTTGGCACAACCTTCACAGCACTTATCATAGCTTGTCATGGTATTTATGACTTA
GCTTCTCACCTTCTTTCAAGGACAGGAAGCTTATCTCATTCATCCTGAATAATCACAACAAAAATAATAGC
TAAAATTATGAGATGTTAGAATGCATATTTTATTTATATGAGGCAATGTGCTAGGTGCTTCCCTTGCACTA
TCTTGTTGCAACCTTTTGACAAACACGTGAGGTAGGTATATCACTGGCCTCCTTTTATAAAGGAAGCTCAG
AGAGATGAATTGACTTTCTGGACTTAAGTTCAGGAAGCTTCACTTCAAAACCCATGCCCTTGACCATGACT
TCACCTTTATTACCTAACTGTGTCTGGGTGAGTTCCTTGTATATAAGTCCTTACTGGGGCCGGGGCAGGGA
GGGGTGTCAAGAGGATGGGACAGTGAAGACAAGAGCAGCCTCCCCAAGGTCATGTGACAAGTCACGGTCAC
ATAAACATCACGAATGCGGGAGCTTTAGCGACCACATTTTCTCCTACACCTTTTACCTAGGAAATGGAAGT
CACAGTTTTCAAAGGGAAACTAAACGTTTTTGACTGTGCAAAGGATTAGATGACAGTATGTTGAATGCAAA
TTGATTGAGTCTGATTTAATTTGGATGGTGATGTGCCAAGTCACACAGCCCTGTTGGACCAGGTGCCTGAA
GCAAAGAACTTTCCTTGCACCCAGCTACCATGGCCTCTGCCTGAGCCTGGGAGGAGACATTTAACAAGGGA
AATTCCTTCTCCCTCCCTCACTGGACTGAACCTGTCCCTTTTCTTAAAGAAAGGGAGTGGCGTGGAGCCCA
GGCCCTCCCCCAGGGGCCTGCCTGCTCAGCTCCAGAC

Fig. 4

NCR2 (natural cytotoxicity triggering receptor 2), Chr6

SEQ ID NO:5

```
tt tagagggagt gaggtgtaga agaaagcaga ctcaactgtg acacagcaga
gaccatctgc ctttccagag cttactgcag ctgaaaagac agataatagt gtgtgggcag
agggtgaacc tggagacttg aaggaaacag gcccctcttc ttggtggaca gtagaggaaa
ataaaggaaa aaatcagggt gaggaaactg accaaactgg gctcaaaatc catgcatgct
cactgacact tttctggcag cagtggccag gagcagactt catccttgtg aggtgggtat
ggcaaccaac cctgcgagta gtgggatggg gaaggggttg cctctgcacc tatgtgcaat
tatgtggcag tctctgacca ccttcctggt ttcctgctct gattgcaggg gggacatatg
gtggaaaacc atgatggagc tcaggagcct ggatacccaa aaagccacct gccaccttca
acaggtcacg gaccttccct ggacctcagt ttcctcacct gtagagagag aaatattata
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gagatgagtt ctgaaacccc ttccccatga ggataagtca ataagcatga actcaacacc
tgcctgtgcc cagctcaggg accaagcacc acaggacaca aacaaaagga gccagcctgg
gaacacagtt gtgagtccat aggtggcggg gcccctgtgc aagattccag cacaggctga
gggaagggga cagtggaggg ggagcaaagc tgaaaatatg tggctggaga gggatagaaa
agcaggacac tagtgggtac cagacagtgg gggaaggagc ccaacaagga tgaggaactt
tgctgtgaag tcatgttagt caggatgcca tgaccttcca tgagcccgaa agagggcaca
cagtcccagg aag
```

Fig. 5

WNT2 (wingless-type MMTV integration site family member 2), Chr7

SEQ ID NO:6

aaacacccaa cttcacttta agaacatcct tcattgatac

aaaggtttgt gatcttggat cagagataat gaactgcaat cctggcacag ttcttggctg

tgcagttaat aatattatgt agatgtttat tgtttttaaa ttttagaatc aaaatttact

tatagttaca gaacagaggt cctcgacttt agtcactcat tcttttatca tccaaataaa

atgtctccag tccctccatc agcggctgtg catgggaaac caccctccca ccccaaccaa

gctccttgcc cagtgcctct gaagacccca gggggagtat cctgccgcta tagcctgttg

ctctggtgtg gcccacttat ccattgatcc attggtattt ggcttggaca ctggccacca

cccatctttc attccctcca aagcagcact agcagagatt gtcactggtg acacattttc

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cctccatagg ccccagactc ccgccacggt gcaggggttt ctcaccttct cctctgcatc

cctgggtctg gatgattctg aaccctgact gcatattaga atcaatcaac tgaggaacca

caagtacctt caaggcccag gcctcacgtc caccctaggt tctaatttgc ccagtctggg

gagaggctgg aaatgatccc caggtgattt taatatgtag ccaggagtga cacctactga

cctgccctct ccagttgcca ggaagaaagc ctcaaattcc tgttatttta ctatgtggag

taatttcacc ctttttgttt cccctctctt tcaagaccat gaaatccctc aaactgtagc

cagattgtaa aagaacattt ttcccttttt ccgccagcta tacacacata tgcaggcctt

taaaaactgg atcataccac atatattgtt ctacattttg cttttatcgc ttgactt

Fig. 6

Probe sequences for methylation array

CAV1:
CHR07FS115953929 115953929 115953978
ATCGACCTGGTCAACCGCGACCCTAAACACCTCAACGATGACGTGGTCAA
(SEQ ID NO:78)

EVX1:
CHR07FS027250107 27250107 27250156
TTGTCACTTCCCGGGCTTCGCGGCGCCAGGTCGGAAATGGTCCCAATGGT
(SEQ ID NO:79)

MCF2L:
CHR13FS112788866 112788866 112788915
TCTTCTCCTGGGGAGGAGGCGTGGCTCGGAGCAGACGTGACTTCTGTTTT
(SEQ ID NO:80)

FGF1
CHR05FS142028596 142028596 142028645
ACAAGCTATGATAAGTGCTGTGAAGGTTGTGCCAAGGGCTGGGGGGATGG
(SEQ ID NO:81)

NCR2:
CHR06FS041426494 41426494 41426555
GTTTCCTCACCTGTAGAGAGAGAAATATTATATCACACTGTTGCAAGGACTA
AGATAAGCGA (SEQ ID NO:82)

CHR06FS041426614 41426614 41426665
GTTTCCTAAGTTTCCTTCAAACTCTGTCTGCATCCGCACATTTGATCTCTAG
(SEQ ID NO:83)

CHR06FS041426769 41426769 41426818
TTATAATCAGGGAAGGGCACTGTACACAAGCCCAGTGAGTAGAAAGGCTG
(SEQ ID NO:84)

WNT2 :
CHR07FS116730563 116730563 116730619
CGGCAGAAGCTGGCATTACATTTCTAAGAACGGGGAAATCGTTATTCAATTA
GAGAT (SEQ ID NO:85)

Fig. 7

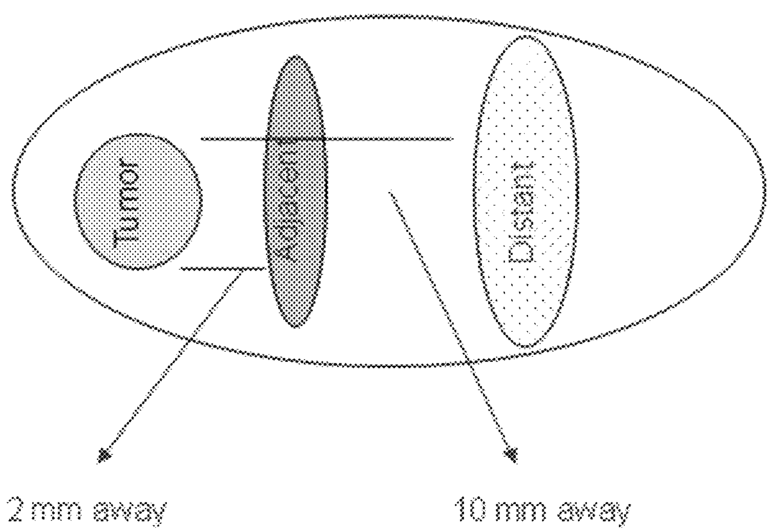
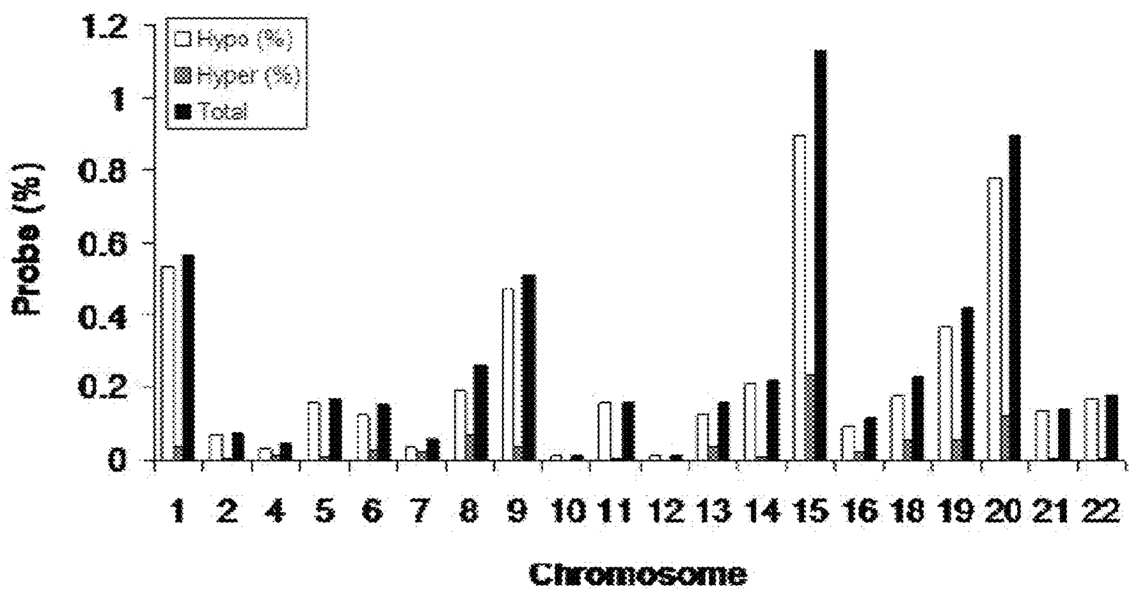


Fig. 8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1
0.8
0.6
0.4
0.2
0
Probe (%)
Hypo (%)
Hyper (%)
Total
1 2 4 5 6 7 8 9 10 11 12 13 14 15 16 18 19 20 21 22
Chromosome

Fig. 9A

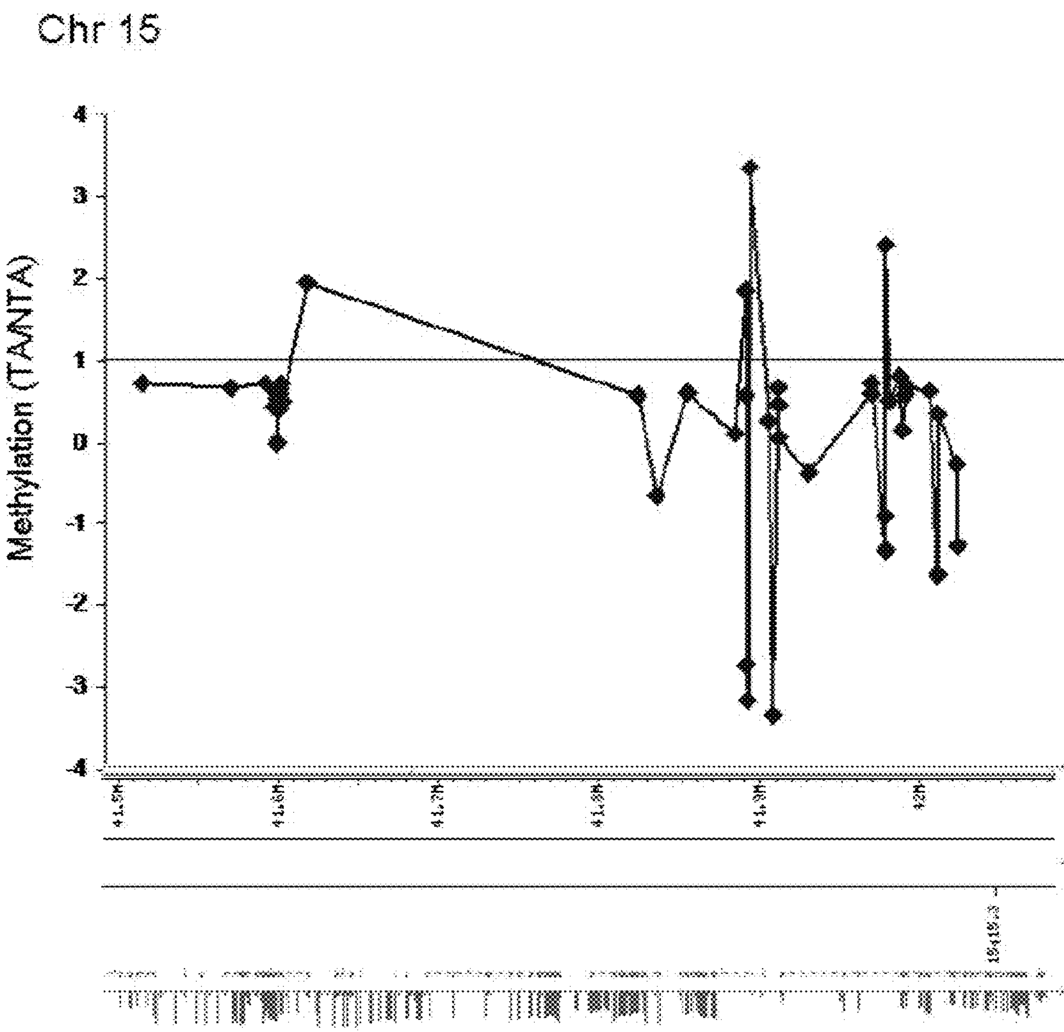


Fig. 9B

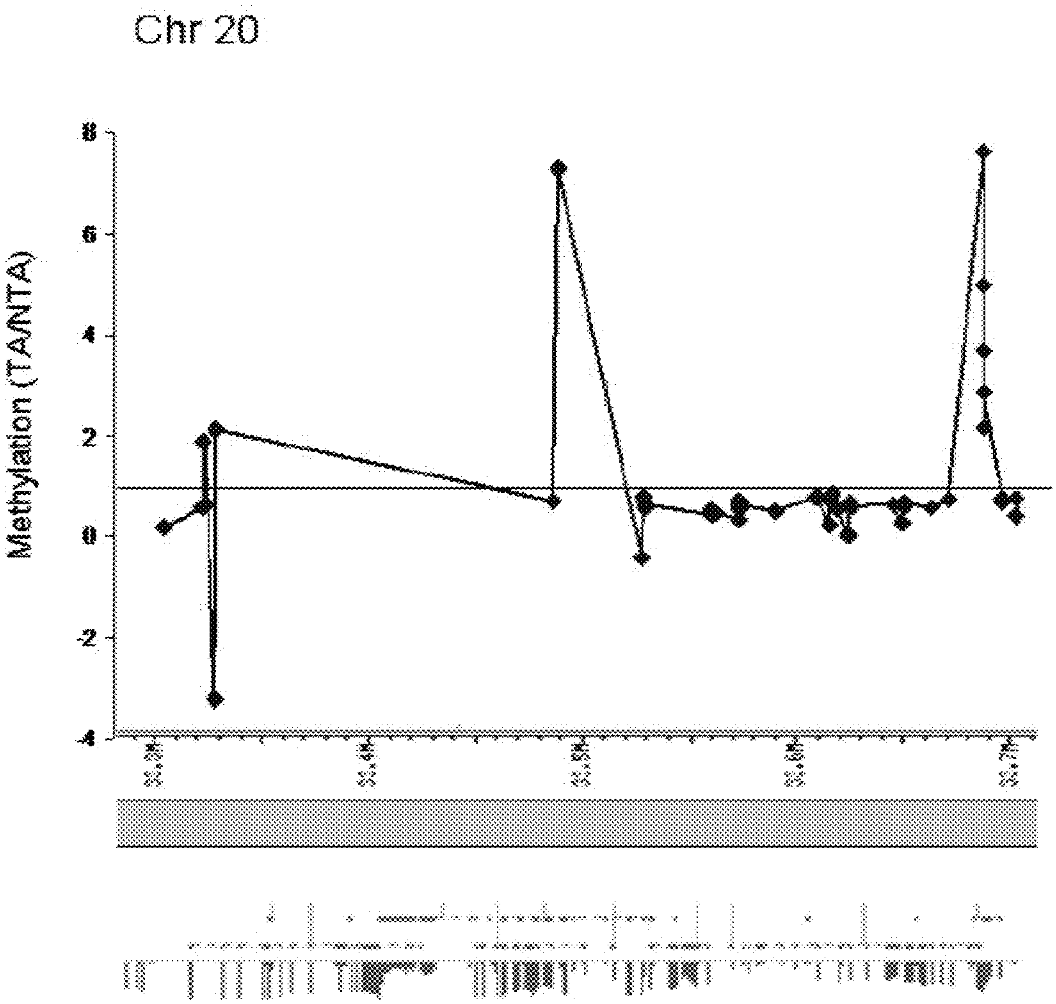
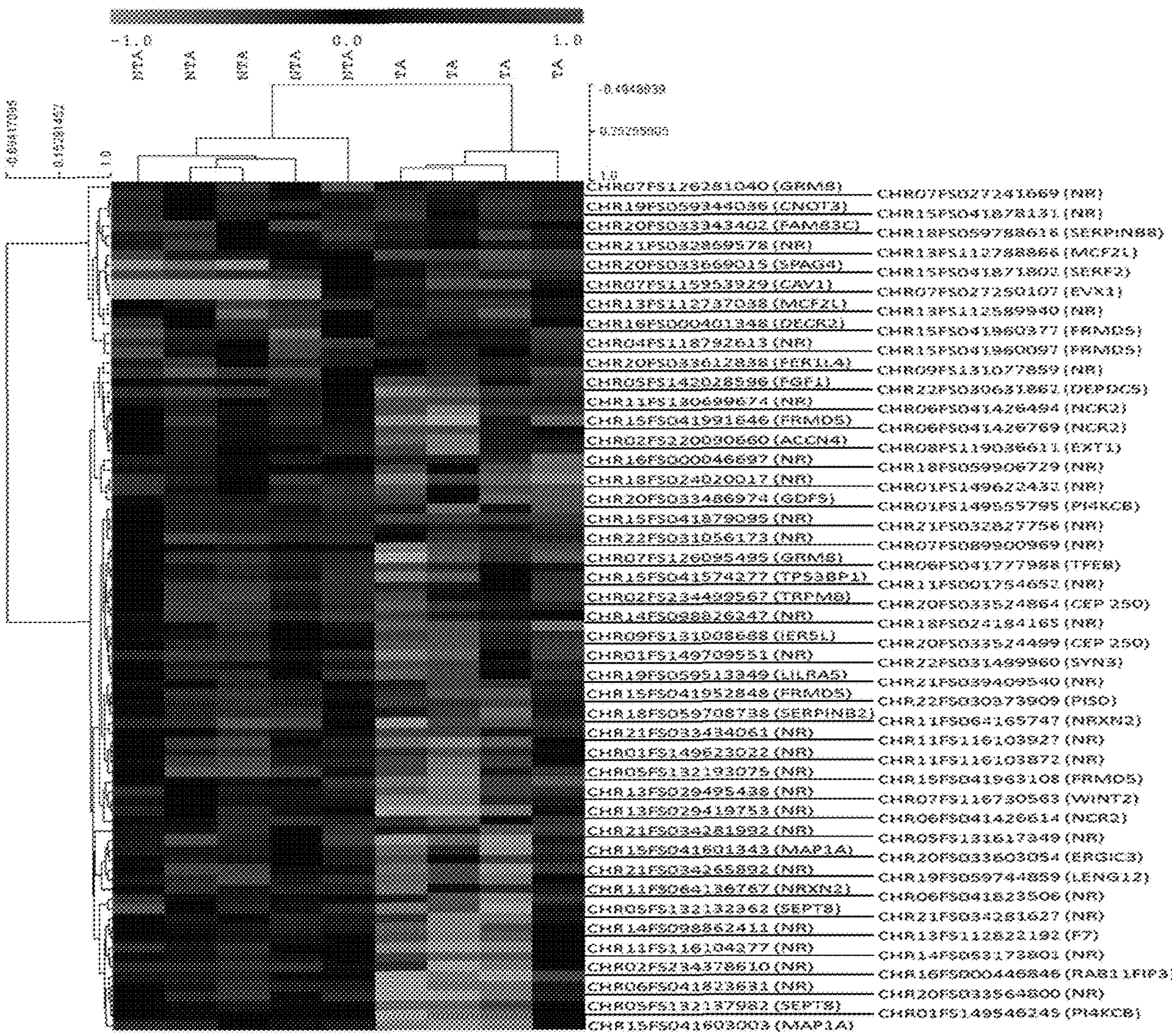


Fig. 9C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NTA
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NTA
TA
TA
TA
TA
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CHR07FS027241669 (NR)
CHR19FS059344036 (CNOT3)
CHR15FS041878131 (NR)
CHR20FS033343402 (FAM83C)
CHR18FS059788616 (SERPINB8)
CHR21FS032869578 (NR)
CHR13FS112788866 (MCF2L)
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CHR15FS041871802 (SERF2)
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CHR13FS112589940 (NR)
CHR16FS000401348 (DECR2)
CHR15FS041960377 (FRMD5)
CHR04FS118792613 (NR)
CHR15FS041960097 (FRMD5)
CHR20FS033612838 (FER1L4)
CHR09FS131077859 (NR)
CHR05FS142028596 (FGF1)
CHR22FS030631862 (DEPDC5)
CHR11FS130699674 (NR)
CHR06FS041426494 (NCR2)
CHR15FS041991646 (FRMD5)
CHR06FS041426769 (NCR2)
CHR02FS220090660 (ACCN4)
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CHR21FS032827756 (NR)
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CHR06FS041777988 (TFEB)
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CHR11FS001754652 (NR)
CHR02FS234499567 (TRPM8)
CHR20FS033524864 (CEP 250)
CHR14FS088826247 (NR)
CHR18FS024184165 (NR)
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CHR22FS031499960 (SYN3)
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CHR11FS064165747 (NRXN2)
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CHR01FS149623022 (NR)
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CHR19FS059744859 (LENG12)
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CHR06FS041823506 (NR)
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CHR14FS098862411 (NR)
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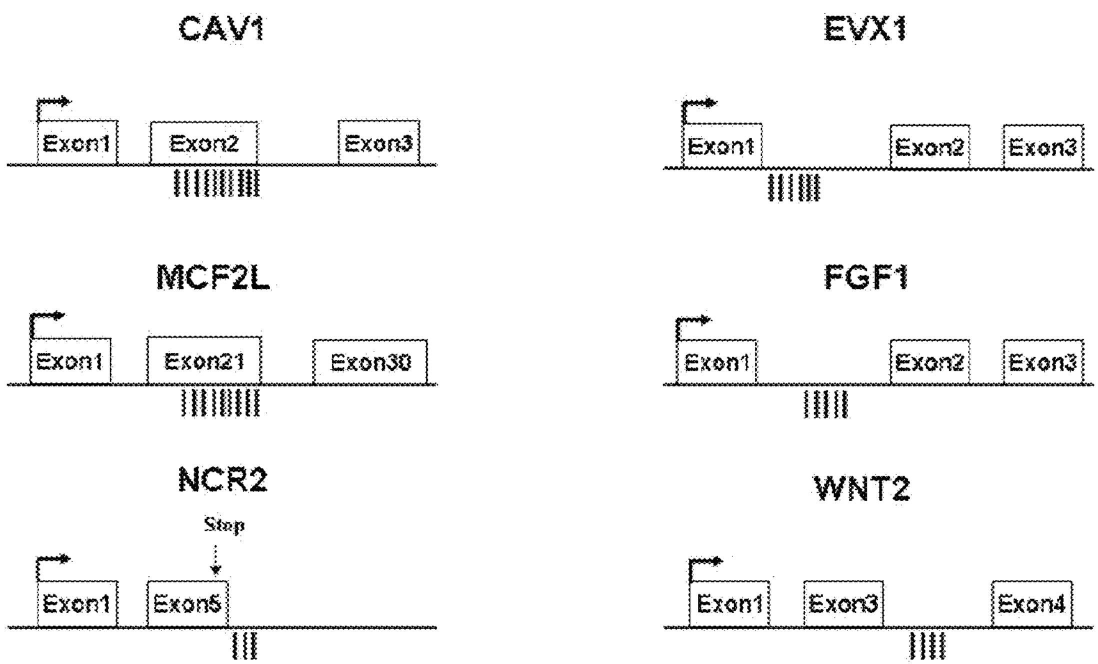
Fig. 9D


CAV1
Exon1
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Exon3
EVX1
Exon1
Exon2
Exon3
MCF2L
Exon1
Exon21
Exon30
FGF1
Exon1
Exon2
Exon3
NCR2
Stop
Exon1
Exon5
WNT2
Exon1
Exon3
Exon4

Fig. 10

Fig. 11A

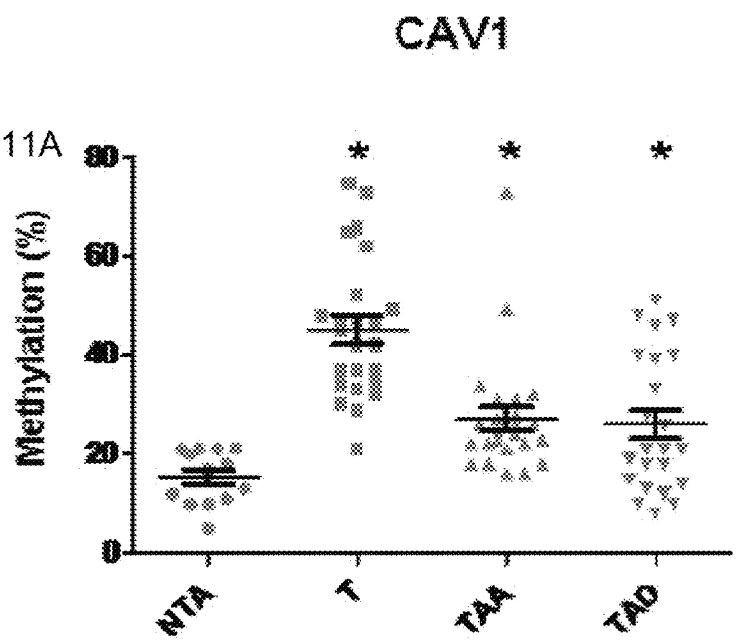


Fig. 11B

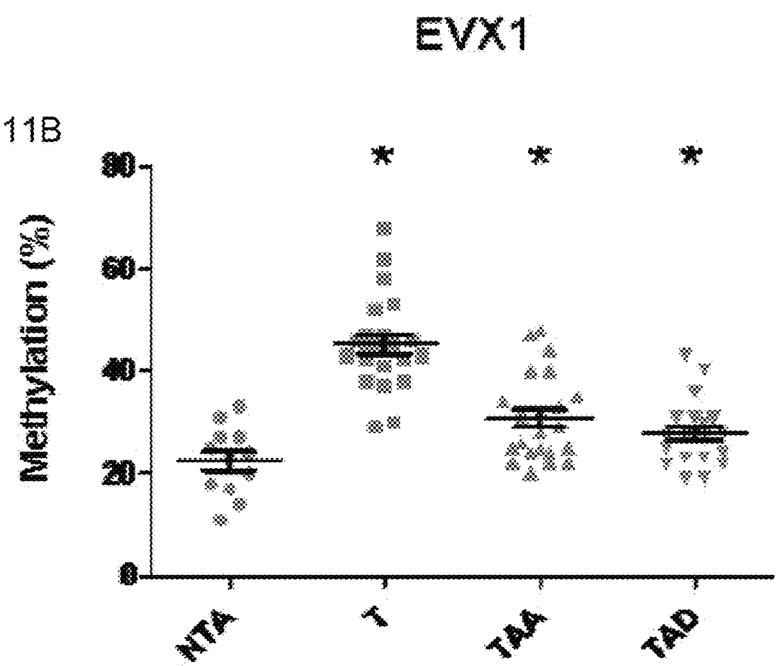


Fig. 11 A & B

Fig. 11C

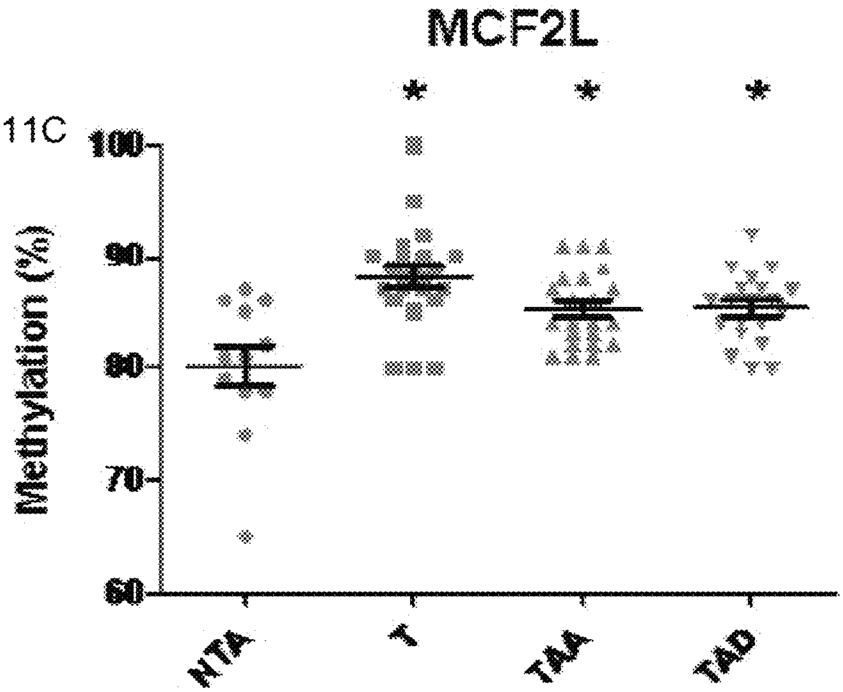


Fig. 11D

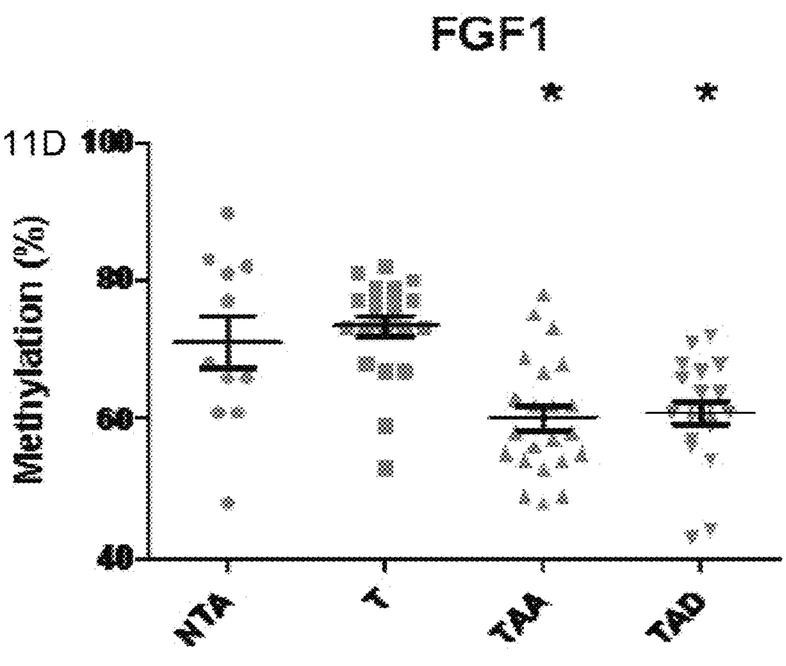
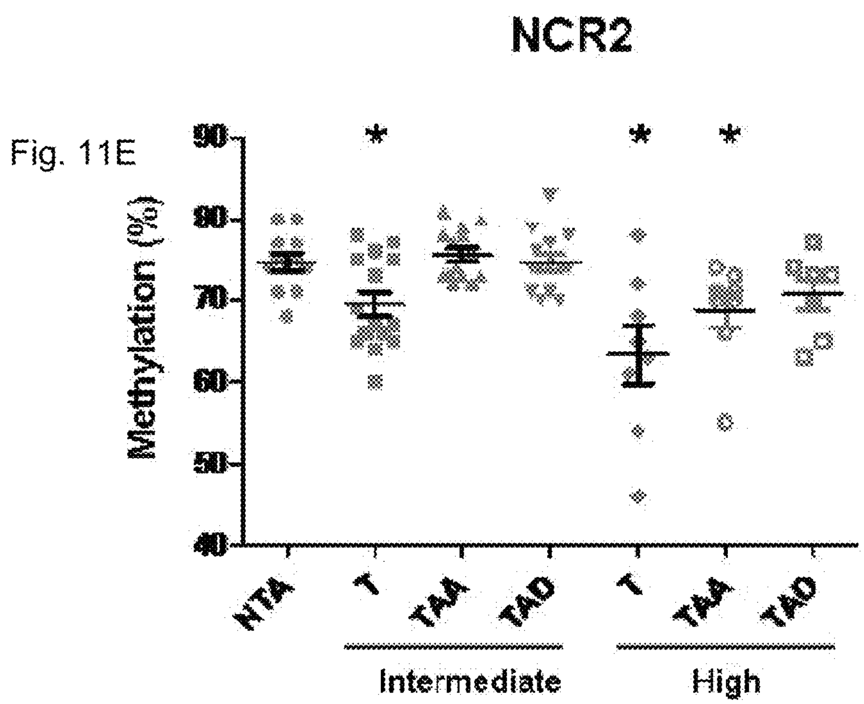


Fig. 11 C & D


NCR2
Fig. 11E
Methylation (%)
90
80
70
60
50
40
NTA
T
TAA
TAD
T
TAA
TAD
Intermediate
High

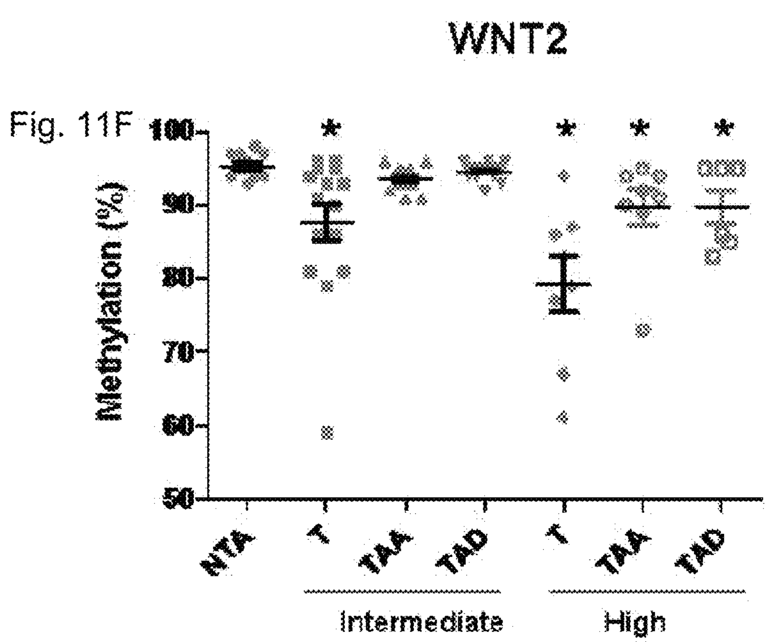

WNT2
Fig. 11F
Methylation (%)
100
90
80
70
60
50
NTA
T
TAA
TAD
T
TAA
TAD
Intermediate
High

Fig. 11 E & F

CAV1	F-GGGTAATATTTATAAGTTTAATAATAAGGT (SEQ ID NO:43) R-biotin-TAAAAACTATCCCAACCCTTC (SEQ ID NO:44) Seq-AAGTTTAATAATAAGGTTATGGTAG (SEQ ID NO:45)
EVX1	F-GGAGGAGAGGAAGTTAGGAGTTTATAAAGGA (SEQ ID NO:46) R-biotin-CAAATACAACCCAAAACCAAAAACAAT (SEQ ID NO:47) Seq-GAAGTTACGAGTTTATAAAGGAT (SEQ ID NO:48)
FGF1	F-GGATGGGATAGTGAAGATAAGAGT (SEQ ID NO:49) R-biotin-TTCAACATACTATCATCTAATCCTTTACAC (SEQ ID NO:50) Seq-TTTTTTTAAGGTTATGTGATAA (SEQ ID NO:51)
MCF2L	F-biotin-GAGTTGAGTTTTATTTTGGGTATTTTGAAG (SEQ ID NO:52) R-ACCCCCAAATTACTAAACTAATATATTCC (SEQ ID NO:53) Seq-CAAATTACTAAACTAATATATTCCA (SEQ ID NO:54)
NCR2	F-biotin-GTTGTGGGAGAGTAAGGTTTGGAAATAA (SEQ ID NO:55) R-CTCATCTCCACCCCCTTCATTTT (SEQ ID NO:56) Seq-CCCCCTTCATTTTCT (SEQ ID NO:57)
WNT2	F-TTTTGGAGGTATAGGGTAGGAAATAA (SEQ ID NO:58) R-biotin-AATTCAAAATCATCCAAACCCAAA (SEQ ID NO:59) Seq-AGGAAATAATTTTTAATTGAATA (SEQ ID NO:60)

Fig. 12

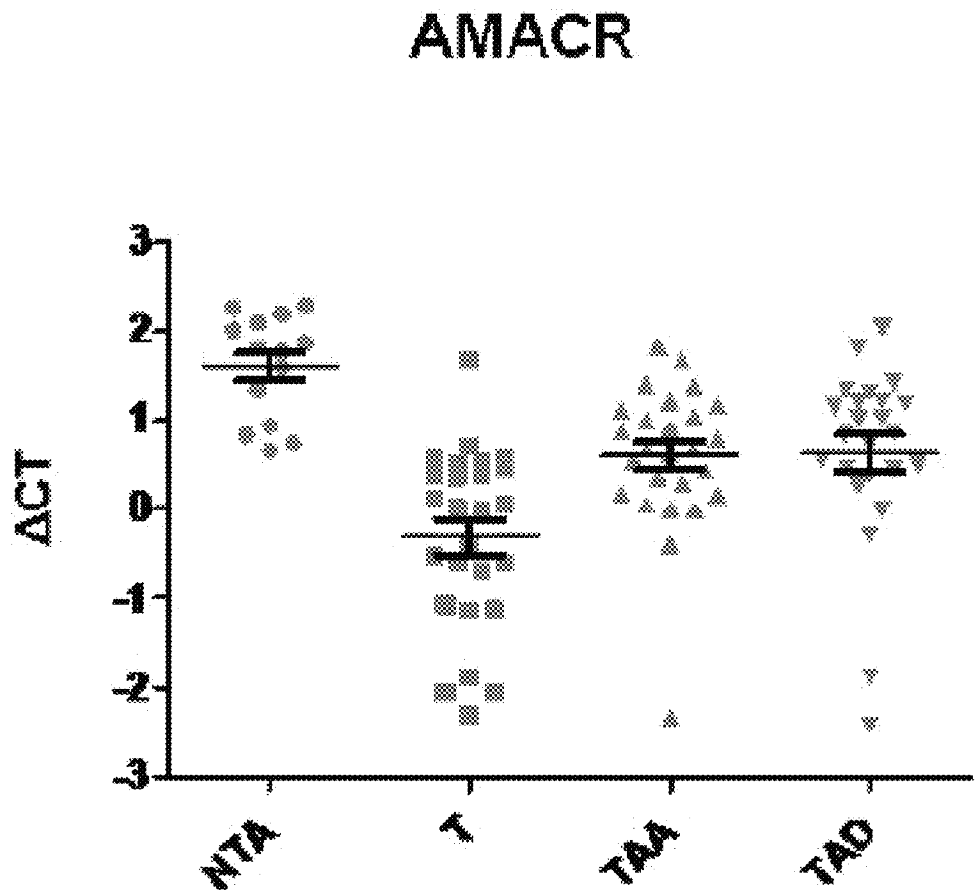


Fig. 13

CAV1 promoter (SEQ ID NO:61)

catgtgtttt aaggcagaga tggaacttgg gcgatgggcg gggggtgggg
gaggtgggaa gggacggctt aggacagggc aggattgtgg attgtttctg
ccgccttggt tgcccatact gggcatctct gcaggcgcgt cggctccctc
cacccctgct gagatgatgc actgcgaaaa cattcgctct ccccgggacg

Fig. 14

EVX1 promoter

Island 1 (SEQ ID NO:62)

agctgccaag gcagaagggg gaagcgggtc ccagaaccac ccacctccgg ctgtccccac

cgcgaggacc cagcagtctg gcgcccccac cacggcctgg aagatgacgg agggcccaag

actaatattc acgacagcca gaccacgctt attgtttaga aggaagctcc ctttgttctt

actttttaac caaagagaag cgaaaacatt tttttcctga tcacattttc accgacacct

gagccgacaa gccagctcct ggcccccggc tcaggactcc tcgctctctc ccttctcggg

gccctgtcgc cgttgaaagg cccgctgcag gctggggagg gtgatcgggg ccgcgggcca

tctcccccga gccgggcggg cagactgcgg aggcaggccc cacacgcgcc gcttttccga

gcccggtttt cttcaggagc gaagctgttc cagctgaccc gcgcgtctgg gggcctatgc

ccggcttccg attccattta aaacgacccg cgcatcttat ctccgtcgcc tccccggggt

tcccacccac ccccctccgg cccgggccag gccagcccag ccccggcgga agccaagctg

ggagcttttg aagtccggag aatttcaatc cgagaggagc cggctggacc ggagcccgtc

gccccagcgg gggaagggac gggggcctg ccgtgtggca ggtgggggat gggtgtcccc

cgccgcgaga aatgagaagc cgccgggcct ggagcggcct ccacctcagc tgctatcacc

ccctctccgc tgtcatggga tt

Island 2 (SEQ ID NO:63)

tttttttgt cttctttcct ttaaaaaccc aaccgctctt aatgtgaggt tgatgaaagg

atgcttttgg aagaagtgac atttggttaa aacgttttcc ccctaatgcg ccggtggaaa

ggggcggggg tgggtgtggt tccctaggct cctaagactg gccagtcagc tttgaaagag

cggggcagaa gtcgggagag gg

Fig. 15

EVX1 promoter

Island 3 (SEQ ID NO:64)

```
cttatgagtc aaacctctat gaaccccaac ctttttgtac tcggggaggc tgaacccctg
cccaaaatag cgcggtgaaa gctactgcct tctcccaagt aggggcctcc agtactgcca
cagcaggggc cgcattcctg gcgcctcttc attcgaaaaa cctctttcca ggagacttcg
ctgattctga acgaatactt
```

Fig. 15 (Continued)

MCF2L promoter

Island 1 (SEQ ID NO:65)

actataagg gggagtactg cgtcaccttc atctttttat ccctttggcc ttgctccgtg
cctgaaagct caccacactg gaacgtccag gtgcacatgt gccactggac accgggatgt
tgccggatgc tcttttggac gctggaatgc tggtgcattg ttgccggatg ctggaatggt
gcacgcacgc tctgttggac gctggaatgc tggtgcattg ttgccggatg ctggaatggt
gcacgcatgc cctgttggac tctggaatgc tggtgcattg ttgccaaatg ccggaatggt
acacggatgc tctgttggac gctggaatgc tggtgcattg ttgccggatg ctggaatggt
gcacgcatgc tctgttggac gctggaatgc tggcgcatgt g

Island 2(SEQ ID NO:66)

a accacaaaag gatagctgcg gttttgggcg aggagagctc agagagtttc ttgcatatgg
ccctgtgatg gcggccatgg ccctgcatag acacgagctg gaatctgcag gtggcagcca
ggacgctgcg tgtgtcgagt gcacagtgtg gcttggtgcc aaccatggcg agggtggaga
gccccgtgcc tgcagcgcgc gcttccctca ctgggtcctg cgtccttggg caggcgatgc
ccctgcgggg aggggctggt ccatccccgg ccagccacgg acccacgcat ggacccagcg
acccacggac ctgcttacct gggcgcggcg cgggtggcat gcggccacac ggaaggggcg
cgctgggctg ctgcggcctc tgcagcttct acacctgcca cggggcggcc ggaggtaaag
ggaggcggcg gccaggcgcg gccccgcgga ggcagctgca ctcgctcggt ccactcgcgg
cttcgcggct gcccgcaaac caggagggcg tggagacccg gaaccggggg gaagggcggg
ggcacttgtg cggcacccgc ggggctccca ggggacctcg gcggtgacac gaatttctag
gtgaccttgg cggtgacacg aatttctagg tgacctgtgt gatacactag gtgacctagt
gacacaggtg acacttccag gtgaccgcgg cggtgacccg cggggctccc aggtgacctc
gttggtgagc cccggggctc cccgacgacc gcggcggtga cacgcggggc tcccaggtga
ccccggcggt gcactcacag gactcccagg tgacccgcgg tggtgacaca ccggggcggg
cgcgcgccgc ttccgcttcc gccgagccgc cccccgcccc ccgcggcgca gcgcgcgccc
ccctcccggt ggcgcggaac caatcctggg cagggaggcg gcggctggag gctgaaagcg
ctgccgtggc cccctccccg cctccgccgc gccccctcc

Fig. 16

FGF1

Island 1 (SEQ ID NO:67)

gcttc tcctgtgcct gcctcatatt ctgggttctc tccagagctc gcgtccactg
cctgccagtc agcagatgga tgactctgtt cacctcagcc gcgacacgcc ccacagcgag
tgcagcagtc gtcctgccag atgggctgct cctggctgcg tccattctct cagtaaatag
cctctccatt catccttccg gtccctctat gcccg

Island 2 (SEQ ID NO:68)

a gccgctcctg tcatcttccc tttctctctc cccatcagcc tgcgagggac taaaagccgg
cgatttttcc ttgctgtatt tctttctttt tttttttttt tttttgagac ggagtctcgc
tctgtccccc aggctggagt gcagtggccc gatctcagct cactgcaagc tccgcctccc
aggttcacac ctttctcctg cctcagcctc ccaagtagct gggactacag gcgcccgcca
ccgcgcccag ctaatttttt gtatttttag tagagacggg gtttcaccga gttagccagg
atggtctcga tctcctgacc tcatgacccg cccacctcgg cctcccaaag tgctgggatt
acaggcgtga gccaccgcgc ccggcctgtt tctttctctt ttttcttgag accgagtctc
gctctgttgc ccaggctgga gtacagtggc atgatctcag ctcactgcaa cctctgtctc
ccaggttcaa gcaattctcc tgcctcagcc ttccgagtag ctgggactaa aggctcccgt
caccaccgtt gcccagctaa ttttt

Island 3 (SEQ ID NO:69)

gattattt tggaatagca cagggttttg ttttttttc gttttttggt ttttcttgag
acggagtttc gctgttgttg ctcaggctgg agtgcaatgc cacaatctca
gctcatcaca acctccgcct cccgggttca agcgattctc ctgcctcagc
ctcctgagta gctgggatta caggcatgcg ccaccatgcc cg

Fig. 17

Island 4 (SEQ ID NO:70)

```
cct ccttcatggg tattccacat tgcttacaca gtgacaggga ttaaaaacaa aactaaaggc
    tgggcgtggt ggctcacgcc tgtaatccca gcactttggg aggctgaggc gggtggatca
    cgaggtcagg agatcgagac catcttggct aacacggtga aaccccgtct ctactaaaaa
    tacaaaaaat tagccgggcg cggtggcagg cgcctgtagt cccagctact caggaggctg
    aggcaggaga atggcgtgaa cctgggaggc ggagcttgca gtgagccgag attgtgccac
    tgcaatccgg cctgggctaa agagcgggac tccgtct
```

Island 5 (SEQ ID NO:71)

```
a tgtattgatg atcacattca ctactcacac ttacaaagta cagctcccag gccgggcgcg
  gtggcttacg cctgtaatcc cagcactttg ggaggccgag gcaggcggat cacgaggtca
  tgagttcaag accagcctgg ccaacatggt gaaaccccat ctctactaaa aatataaaaa
  ttagcctggt gtggtggcg
```

Fig. 17 (Continued)

NCR2

Island 1 (SEQ ID NO:72, located between exons two and three)

gtt gtgaacttgt gtttttccgt tttatatgta tatgccactt gtttttttgt tttgttttat
ttcgttttga ggcggagtct cgctctgtct ggagtgcagt ggtgcaatct cggctcactg
caacctccac ctccagggtt caagcgattc tcctgcctca gcctccggtg tagctgggac
tacaggcgcc tgccacc

Island 2 (SEQ ID NO:73, located between exons two and three)

aag tagctgggat tacaggcgcc tgctaccacg cctggctaat tttttgtatt ttagtagaga
cgtggtctca ccatgttggc caggctggtc tcaaactcct gacctcaagt gatccacctg
cctcggcctc caaaactgcc gggattacag gcgtgagcca ccacgcctgg ccgctaacaa
gtaattttaa agtatca

Island 3 (SEQ ID NO:74, located between exons four and five)

tttaactttt tgaacttttc cgaagctttc catattttct atgtcctcca agtgcccatc
atatctttta ttttctcctt tcattgacct ctgtctttct tcagagcttt ctggaaacct
ttgccgcttc tcggccaccc acttgcttag aagccccatg cgggccgcgg ggtgctgtgg
gctccaggcg gattgggcgg g

Island 4 (SEQ ID NO:75, located between exons four and five)

ccagaatcc caactcagta agaccttgta aatccatgac attagcccca attcccactc
gtcccaaatc ccataacctt tccaccctgc acctgaagtg cgcagtcatc agcacaagct
cctgtatgct cagcttctct gaacgtcacc gcggtactct ccctgacatc tgcctgttct
ccgaggacaa tgctttctcc g

Fig. 18

WNT2 promoter

Island 1 (SEQ ID NO:76)

gc caaccacctt ttctttccta agtgtctgga tttacttcaa gaaaatgcgg gacaaagaag
ggtggaggta agctttcgtt tattcccctg cttcacgggg gaaggaggtt tgtgagcata
agcatgtaag tacatgagag gcgtgttgct ctttggtgcc tatcataccc tccccatggc
cggcgtgcac acacggcgag cagaaacgct cccccgcccc gctgcctgcc gccccacgcg
ccctccctgc acctcccgcc cgaccgacgc agaccaagca gaacttccct gggtcgcggc
ccagcgatac ggagcggccc tggcgaggag ccctgctctt cccgagtcgt gggtggcgcg
gtgcttgttt ccctcccctc cctttccgga cccaaacggg gatgtatctg ggtcagcctg
ggagggggccg gacctgccag ggaccagcgt gggggaaggg ggtggcgatg acagcatctt
tcaggttttt ggcgtctctg agcttcgcct cgtccagcct ctcaccgcgc tcgctgccgg
cgagggctga cgctctggcc agtccaggcc cgagggtggg ctggagagag ggagagcccg
tccttccgat ctgggcggca ccccctcccc cacgccctgc gaacaattcg cctcccacac
atacacacag gcgcatactc tattccccag agcacgctcc tcgggcgggc agtgagtccc
tccgccccag gaaaagagca atggaacagt tcacggccgc cacgagttcc tggtcttcct
tcctttccgg tgataaacgg cgcggctaca agccagctac tgctcaaaat gctccacccg
cgggcccaag cccctctctc ttggctgggc gggggcccag gtccaggacc gagggtccct
taacctccac aaggcgcaca ggctgagcgc ccaggcggca ggaggtgcaa gggcgcacac
ccccggcgaa cgcctggctg cctcggttcc tctctatgtg

Fig. 19

Island 2 (SEQ ID NO:77)

```
ataga cgcggcagct ccaaatttac aagtgctagc tcttcatccc agcttcaggg agagaagcga
      agcaatgagt tgagaatcat ctctggattc ttgtatccca tgcatagtaa tctccttatc
      ccctggcccc cttcctcgtt tcctcacatt gcacgctcag ggacttgttt gccagcggat
      ggcctcggca atccggaacg cacgctccga gagcccacgg atgctctttg gcctggagct
      tccctaaagg ttcctgtatt cgcgtgtgct cgtaaccatg cagcgatgtt ccccttccc
      cgcctcacct catccccaga catctcttgc catcatttca tgcacccgtg tctaaaccc
      cgcgtttctc cccaccccg ccaggcgcag caccc
```

Fig. 19 (Continued)

EXT1 (exostosin glycosyltransferase), Chr8

SEQ ID NO:18

catcttttg agtattgttt attgtaatgt aagaaccagt catgcctggg
gtacactcaa gctggatcct tgccataagg gcaggctggg gtgaatggtg
gtacactctt ggtaaatgtg acatgataag aaatatatat ttgggccagg
cacattgtcc tgcacctgta atcacagaac ttggggaggc taaggcaggc
aaattgcttc aggccaggag ttagagacca gcctggccaa catggtgaaa
acctcctctc aactaaaaat acgaagatta gctgggcgtg gtggctcctg
cccgtagtcc cagctactcg ggaggttgag gcatgagaat cgcttgaacc
cgggaggtgg aggttgcagt gagctgagat cacaccactg ctttccagcc
tgggcaacag agtgagactc tgtctcaaaa atttggtctc tgccccttga
cacccaactg ctaaaaccct tgtaatttcc tgagtgatag aggtgataag
aatgtcttcc acagaattcc caaatccctt ggaatttcct gggtgataaa
ccttttgttc taatgaggtg attcttagtg ggttcctgga tagcttcaaa
gtggtgatgt catcagaaag actaaactgt cattagaagc ttggaacttc
taacccaccc tacccctatt ctccagggag gagagagggg ctggaaattg
tttaattatc tatcatgcct atgtgatgaa accccctcaa aatttctaaa
ctatgaggtt tggagagcct ccaggttgat aaccatatcc acatgccggg
aggatggtgc accccgactc catggggata gaagcctctg tgtttgggac
ttttctggac atcacacagt gtacctcttc atctggctgt tcatgtgtat
ccattatgtc ctttttaata aatcagtaat agtaagctgt tttcttgagt
tctgtgaccc cttctagcaa acgattgaac ttgaggaggg agtcatgaga
tcccctgact tgtaggcagt tggtgagaag tataggagac ccagacttgt
gattggcatt tgaagtgagg gataatcttg tggctctgag cccctaacct
gtggtgtctg cattaactct gggtaattac tgtcagaatt gaattcaatc
attagatatc aagtaggttt ccaggaagtt ggagaacttg ttgttggtgt
gaggggaaga aacccataag tttggtgtca gagcattgcc agtagagaaa
caggtccccc ccacatatga gttggatggt gttatgctct tggtagggca
tttgttttga

Fig. 20

SPAG4 (sperm associated antigen 4), Chr20 T

SEQ ID NO:39

```
  tctcccga ccctggatct gaggcaggag atgcctcccc cgcgggtgtt
caagagcttt ctgagtacgg gccaggccag ctgcgatccc ctctgaccct
cgggttcccc tctccgaact ccagttctct ctgagccccc ggcccccgtt
tgagtatcga gcccctctcc gagcctcaac tcattcctag cccccatcca
attatcctag ccgaccctct cttcctgagc cccaggccca cccccggccc
ctcccaagcc ccttctgaac ccggacacca cgcaggctga gccccgcctc
tccctgccgt gggcccctct ctgaccctct gtcctggcct caggcctgct
cttccagggg ctgagcgtgt tgttatccct ggcaggagac gtgctggtca
gcatgtacag gtcagaggaa gggacgctgg cgccccagga acagctcttt
ggagggggtg gggagcaggg ccggaacctt gctggcgctt gagccgattc
agatctgatt gagtcatgtt ggcaagagct gggtctagga ccctggggtg
gggactggag ggttgagcag gtcggggcct cagcctccct ccggttcccc
agggaggtct gttccatccg cttcctgttc acggctgtgt cgctgctgag
cctctttctg tcaggtgagg ggcagtgaat tccctggagc ccctgccctg
ggtgctttgg aggcaaaccc agcacatttt ctcctacatc ctcggtcctg
cagctcctgg cattcccctg cagaacccccc taattccccc tcagactccc
acggtcctcc ccaggcttaa ccccctcaag cctctttcca ctgtccccct
atgccgggga aacccattct cttccttttc cttctgagac ccctccctct
ctttctccag cattctggct ggggcttctg tacctggtct ctcctttgga
gaatgtgagt tggggagact gtcttggggt agggggttgg caggttgtga
acccggagat tgtgggggtc ccctggactg tcggtctgct ggggtggggg
ta
```

Fig. 21

Probe sequences for methylation array

EXT1:
CHR08FS119036611 119036611 119036660
CACCATCCTCCCGGCATGTGGATATGGTTATCAACCTGGAGGCTCTCCAA
(SEQ ID NO:86)

SPAG4:
CHR20FS033669015 33669015 33669064
ATCTGATTGAGTCATGTTGGCAAGAGCTGGGTCTAGGACCCTGGGGTGGG
(SEQ ID NO:87)

Fig. 22

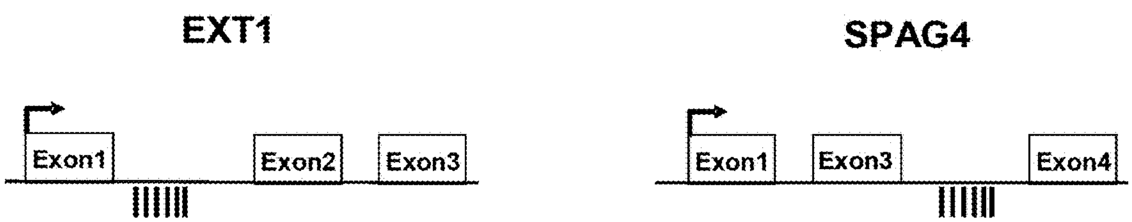


Fig. 23

Fig. 24A

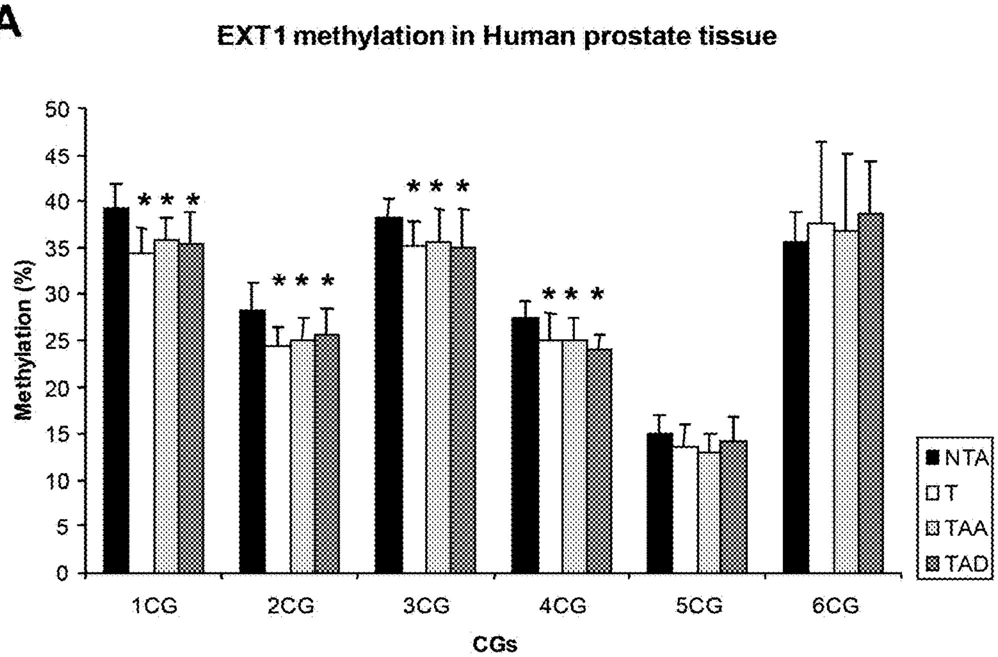
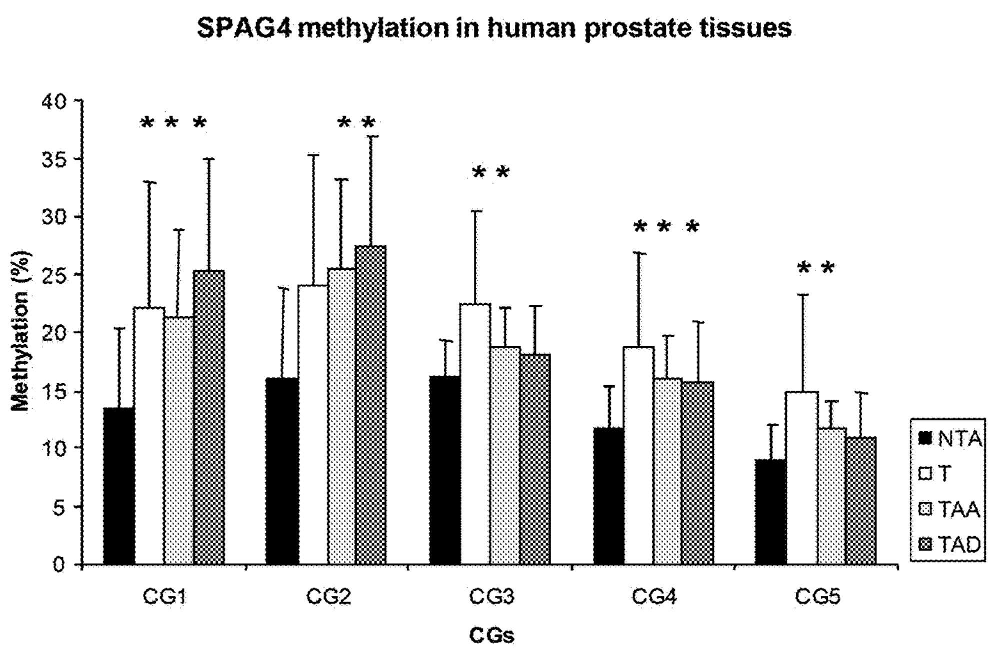


Fig. 24B



EXT1	F-TAGGAGTTAGAGATTAGTTTGGTTAATATG (SEQ ID NO:88) R-biotin-CCAAATTTTTAAAACAAAATCTCACTCTAT (SEQ ID NO:89) Seq-CAACTCACTACAACCTCCA (SEQ ID NO:90)
SPAG4	F-GGTAGGAGAAGTGTTGGTTAGTATGT (SEQ ID NO:91) R-biotin-CCTAAACCCAACTCTTACCA (SEQ ID NO:92) Seq- TTAGTATGTATAGGTTAGAGGAAG (SEQ ID NO:93)

Fig. 25

EXT1

Island 1 (SEQ ID NO:94), 458bps

CGTCCTCCCCGCGGGCAGTGCCGGCCCCGAGCAGCGCTTCGCAGGCCCCC
GCGCGAACGCTGCCGACCGCCGCGTTCGGTCGCCGAATGTTACCCGGTTC
TGAATGTTACACTTACACATTCCATTCCCGACACGACAGCGCTGACCTCA
TCCATCCACGCAGCCCGCGCTGCCATTGGCCGAGCGTCACGTCCGGGGGG
GGCGGTGCTTCCGCTGCGCCCATTCATAACCCCCGGCCGCGGGCCGAGGC
GCCGGCGCGGCGTTGGGGGCGTAGGGGGCGCAGGGAGCCGGGGCTCCCGG
GTTGCAAGCTGCCGGCGGGCTGCCGGGCAGGTGGAGCGCGGGACGGCCCG
GTGCGAGCCCCGCGGCCCCTCGGCGCGCCCAGGCCCGGATCTCGGCCTGC
GCCGTGCCGGGGACCAGAGGCGCCTGCGGAAACGCGGCGGCCGGGGAAGG
AGGCACCG

Fig. 26

SPAG4

Island 1 (SEQ ID NO:95), 2190 bps

GAGGTCAGGAGTTCACGACCAGCCTGGCCAACATGGTAAAACCCCGTCTC
TACAAAAATACAAAAATTAGCCAGGCATGATGGCGGGTGTCTGTAATCCC
AACTACTCGGGAGGCTGAGGCAGGAGAATCGCTTGAACCCGGGAGGCGGA
GGTTGCACTGAGCCGAGATTGCACTACTGCCCTCCAGCCTGGGCGACACA
GCAGGACTCTGTCTCAAAAAATAAAAATAAAATAAAAATAAAAATGCTGG
GCGCAGTGGCTCATGCCTGTAATCCCAGCACTTTAGGAGGCCGGGGCGGG
TGGATCACCTGAGATCGGGAGTTCAAGACCAGCCTGACTAACATGGAGAA
ACCCCGTCTCTACTAAAAATACAAAATTAGCCAGGCATGGTGGTGCATGT
CTGTAATCCCAGCCACTCAGGAGGCTGAGGCGGGAGAATCGCTTGAACCC
GGGAGGCGGAGGTTGCAGTGGACCAAGATCGCGCCATTGCACTCCAGCCT
GGGCAACAGAATGAGACTCCATCTCAAAAAAAAAAAAAAAAAGAAAGAAAG
AAAGAAAGAAAGAAAGAAAGAAAGAAAGAAAGAAAGAAAGAAAGAAAGAA
AGAAAAAAACTGTTATAGACTGAGTGCCATTTTAGATGGGGTTTTCTGGG
AAGTGCTGTGACATCATCGCTTGCTGTAAAAGAGGCCGGGCGCGGTGGCT
GACGCCTGTACTCCCAGCGCTTTGGGAGGCCGAGGCGGGAGGATCGCTTG
AGCCTAGGAGTTCGAAGTTACAATGAGCTATGATCAGGCCACTGCACTCC
AGCCTGGGCAATGAGAAAGACCCTGTCTCTTAAACAACAACAAAGTCAGA
AGGAGAGGCTGCCATGGCTACGGCTCCAGGTGACGTCACGGCCAGCTCCG
TGACGCGCGGCCAGGGCAGCCCGCGGAGACCGAGGCTCCTCTGTGACGTC
AGCAGCCGGCCGGGACACAGCGGGAGGGCAGGTGCGGCCGCGGGGCCTGC
CGACTTCACGCAGGGTCCGTGGGGTCCCCGCGGCGCGCAGCGGCTGAAGG
AGGCCCCAGGGCCTTGGCGACCGCAGCGGCGGCTTTAGCGTCAGTGACTA
GGCAGCAGGGGGTCAGGATGCGGCGAAGCTCCCGCCCGGGCTCGGCCTCG
TCCTCGCGCAAGCACACGCCCAACTTTTTCAGCGAGAACAGCTCAATGAG
CATCACCTCGGAGGACAGCAAAGGGCTCCGGTCAGCGGAGCCCGGGCCTG
GGGAGCCCGAGGGCAGAAGAGCCCGGGGCCCGAGCTGCGGTGAGCCCGCC
TTGAGCGCGGGAGTGCCCGGAGGAACCACATGGGCAGGAAGCTCTCAGCA
GAAGCCAGCGCCTCGGAGCCACAACTGGCAGACAGCCTGTGGCGCGGCAA
CCGTGAGGGGCGGGGCCTCGGGTGCGGGCGGGGTCGACCCCGGGTGAGCC
AGTGGAGGGGGCGGGGCCTAAAGGGCGGTGCTGGGCGGGGACGGGGCTAA
GATGATATCTGGGCACCTCCTACAAGGTGGGTCCTGTAGGGTAAAGGGAT
GGTGCTAAATGAGATCCCTTAAGGGGCGGAGCCTCGGTGTCCTGGACGGT
TATGGGAAGGGGCGGGGAAAATCTTGTGGTTGGGTGCCACTGAGGGGGCG
CGGCCTCAATGTTAGCGTGAGTGGCTCCCAGGACAATTGGGTTCCACCAA
GATCTAAGGCTGGGGGCGGGTCATCCGTTTGGGGGAGGGACCAACTCTTT
TTTTTTTTTTTTTGCAACGGAGTTTCGCTCCTGTTGCCCATGCCATGCAA
TGGCATGATCTCGGCTCACCGCAACCTCCGCCTCCCGGGTTCAAACGATT
CTCCCGCCTCAGCCTCCCGAGTAGCTGGGATTACAGGCGTGCGCCACCAT
GCCCGGCCAATTTTTGTGTTTTTAGTAGAGACGGGGTTTCTCCGTGTTAA
TCAGGCTGGCCTCGAACTCCCGACCTCAGGTGATCCGCCCGCCTCGGCCT
CCCAAATCGCTGGGATTACAGGCGTGAGCCACCGCGCCCGGCCAGGAGAC
CAACTCTTGACGGAGCCTCCCTGAGGGGCGGGGCTTCAGAGGGCGGAGCT
GGAGCCGGGATAGGGCTGCGGTGGACCAAAGCCTGTGAGAGACTTCCCA
GCTGTCTGGCTTGTGGACTGAGCAATCTGCGGCCCGGTCT

Fig. 27

SPAG4

Island 2 (SEQ ID NO:96), 282 bps

CGGCCCGGTCTCGAGGGGAAAATAGGTCTGTGGTCCGCAAGGCCCCAGTG
GAGCCCTTGGGTTCCCGCAGAACCGACTGGGTCTCCAGTAGTCTCTGAGG
AGCCGCTCGACCTTCTCCCGACCCTGGATCTGAGGCAGGAGATGCCTCCC
CCGCGGGTGTTCAAGAGCTTTCTGAGTACGGGCCAGGCCAGCTGCGATCC
CCTCTGACCCTCGGGTTCCCCTCTCCGAACTCCAGTTCTCTCTGAGCCCC
CGGCCCCCGTTTGAGTATCGAGCCCCTCTCCG

Island 3 (SEQ ID NO:97), 234bps

CGGCAGCAGTCGCTCTGTCCGACGGTTCCGATGGTCCCTCCGCCCGCCTG
CAGCCCCACGTGTTCCCTGGGAATTGCTGGGCTTTTGAAGGCGACCAAGG
CCAGGTGGTGATCCAACTGCCGGGCCGAGTGCAGCTGAGCGACATCACTC
TGCAGCATCCACCGCCCAGCGTGGAGCACACCGGAGGAGCCAACAGCGCC
CCCCGCGATTTCGCGGTCTTTGTGAGTGCGGACG

Fig. 27 (continued)

Fig. 28A

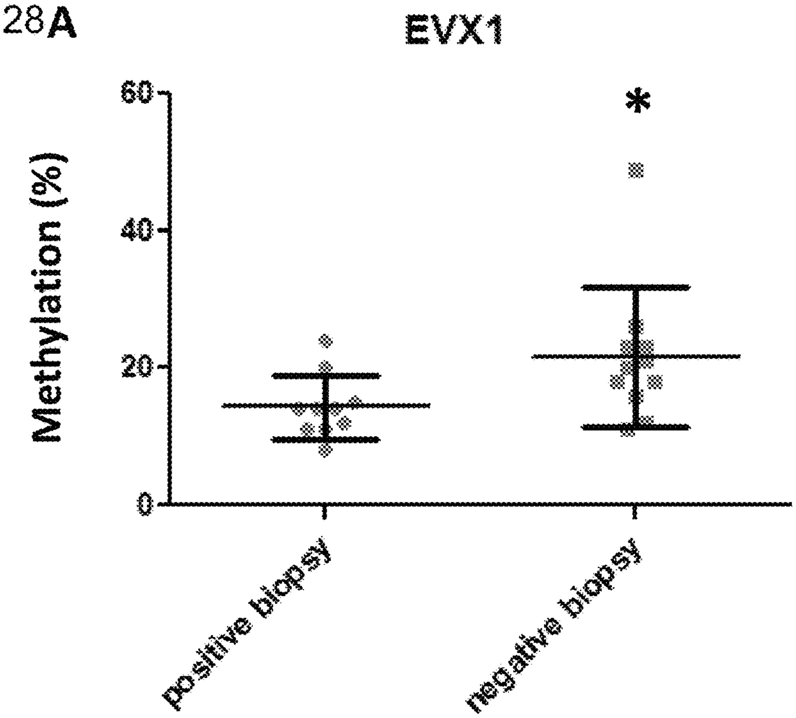


Fig. 28B

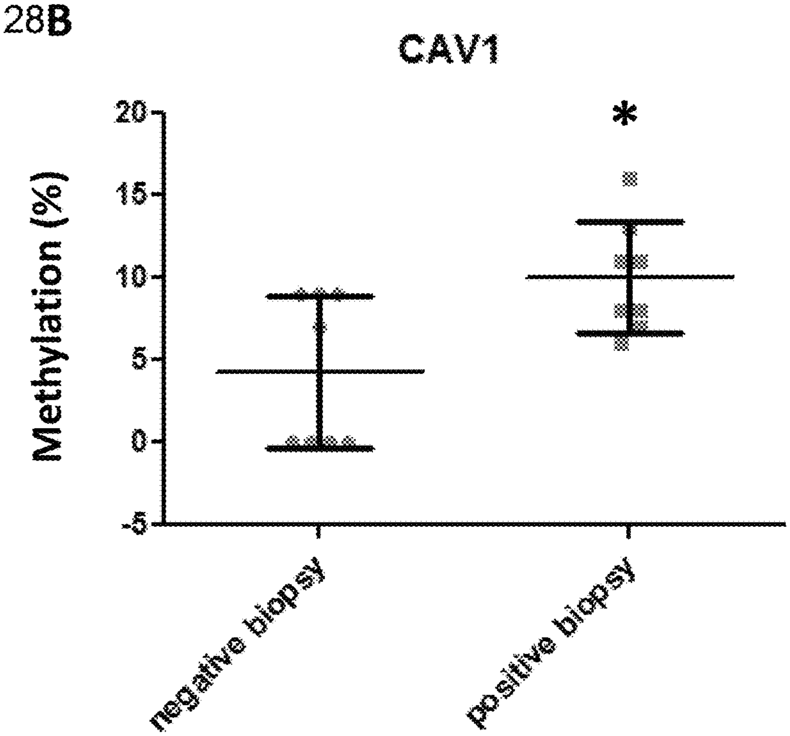


Fig. 28C

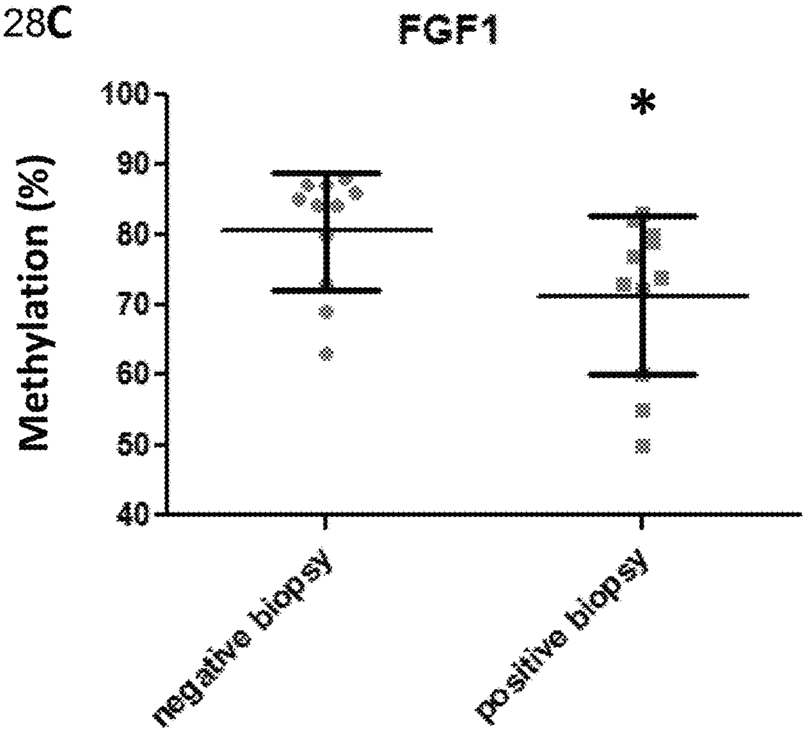
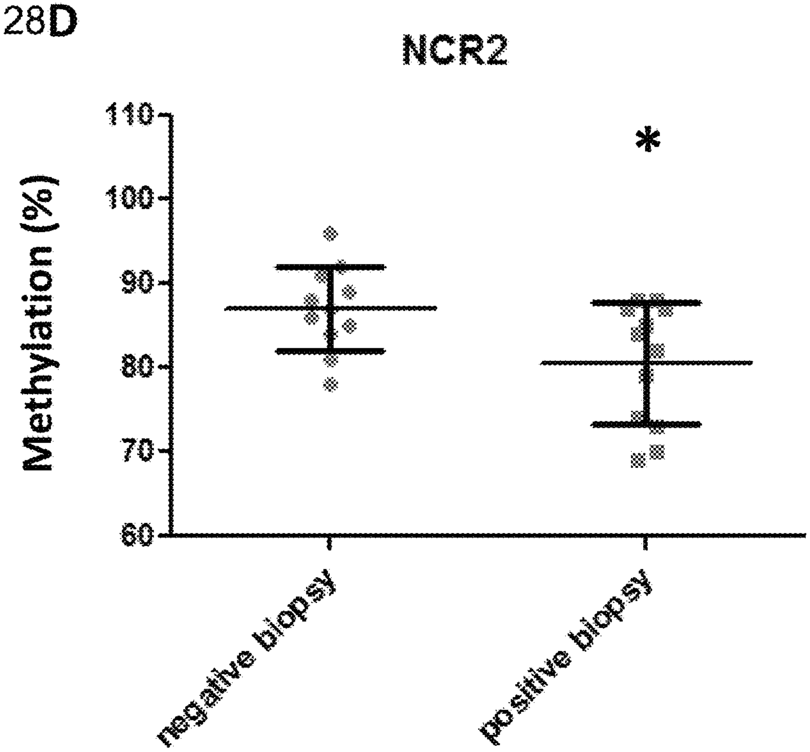


Fig. 28D



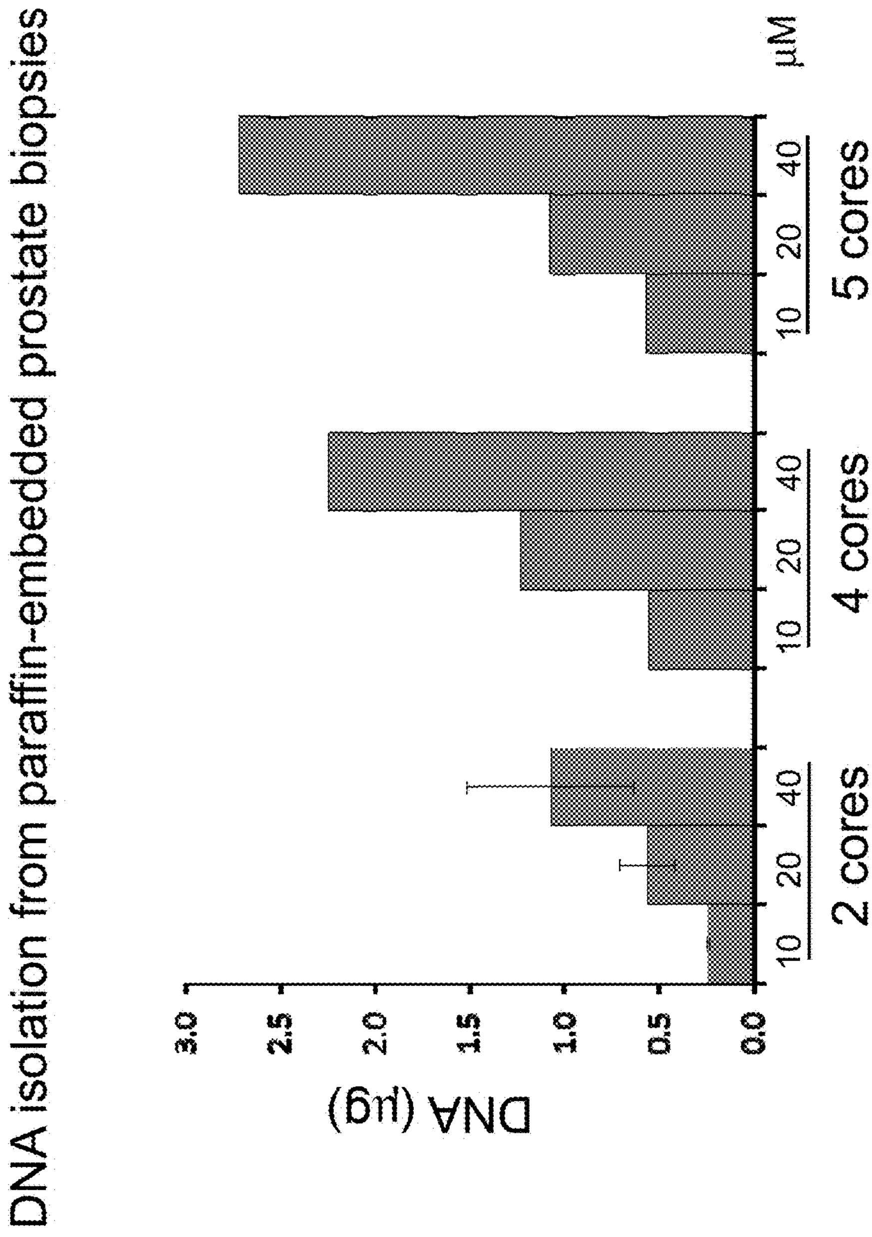

DNA isolation from paraffin-embedded prostate biopsies
DNA (µg)
0.0
0.5
1.0
1.5
2.0
2.5
3.0
10
20
40
2 cores
10
20
40
4 cores
10
20
40
5 cores
µM

Fig. 29

UNBIASED DNA METHYLATION MARKERS DEFINE AN EXTENSIVE FIELD DEFECT IN HISTOLOGICALLY NORMAL PROSTATE TISSUES ASSOCIATED WITH PROSTATE CANCER: NEW BIOMARKERS FOR MEN WITH PROSTATE CANCER

CROSS-REFERENCE TO RELATED APPLICATION

This application claims the benefit of U.S. Provisional Patent Application Ser. No. 61/806,218 filed on Mar. 28, 2013; U.S. Provisional Patent Application Ser. No. 61/806,566 filed on Mar. 29, 2013; and is a continuation-in-part of U.S. application Ser. No. 13/288,607 filed on Nov. 13, 2011. All of these applications are incorporated by reference in their entirety.

STATEMENT REGARDING FEDERALLY SPONSORED RESEARCH OR DEVELOPMENT

Not applicable.

BACKGROUND

It is estimated that 198,280 men were diagnosed with prostate cancer and 27,360 men died from prostate cancer (PCa) in 2009 in the USA (Jemal et al., (2009) *CA Cancer J Clin* 59, 225-249). The predominant tools for early detection of prostate cancer are prostate specific antigen (PSA) testing and digital rectal exam (DRE). However, 65% to 70% of men with total PSA ranging between 4.0-10.0 ng/ml have a negative prostate biopsy result. In addition, 15% of PCa patients have PSA levels <4.0 ng/ml, indicating a weak predictive ability (Thompson et al., (2004) *N Engl J Med* 350, 2239-2246). PSA-based screening also detects non-significant cancers leading to an estimated 50% of overdiagnosis (Fritz et al., (2009) *The New England Journal of Medicine* 360). A urine-based test examining an RNA molecule termed PCA-3 is currently undergoing FDA trials. Prostate biopsy is used to confirm disease. However, because of sampling errors repeated sets of samples are commonly required to make a diagnosis (Gann et al., (2010) *JCO* 28, 7). Typical biopsy schemes include 10-12 or more tissue cores removed under local anesthetic. Re-biopsy is often required two to three times in order to rule out cancer because of sampling errors. Cancers can also be missed because of sampling problems.

There is a clear need for biomarkers that allow easier and more accurate diagnosis and prognosis of prostate cancer.

SUMMARY OF THE INVENTION

In one embodiment, the present invention is a method of detecting the presence of a prostate cancer field defect in a human subject comprising the steps of obtaining genomic DNA from the human subject, amplifying at least one target region, and preferably at least two, three or four regions, selected from the group consisting of CAV1, EVX1, MCF2L, FGF1, NCR2, WNT2, EXT1 and SPAG4 target regions, purifying the amplification product; and quantitating the methylation in the target regions, wherein significant methylation changes indicate the presence of prostate cancer field defect, wherein the change is relative to tissue from a second human subject who does not have prostate cancer.

Preferably, the significant methylation change is $p<0.05$ or at least ±50% of the pyrosequencing percentages or fold-changes shown in Table 1.

In another embodiment, the present invention is the amplification product described above.

In another embodiment, the present invention is a combination of the amplification product described above and materials useful to determine methylation status.

In another embodiment, the genomic DNA is obtained from prostate tissue. In another embodiment, the genomic DNA is obtained from body fluid preferably selected from the group consisting of urine and semen. Most preferably the bodily fluid is urine.

In a preferred embodiment, primer sets are used for amplification of the target region and at least one primer within each set of primers is biotinylated.

In yet another preferred embodiment, the methylation is quantified via pyrosequencing.

In another embodiment, the quantitation of methylation comprises analyzing whether the CAV1, EVX1 or MCF2L regions are hypermethylated or FGF1, WNT2 or NCR2 regions are hypomethylated as a positive correlation to prostate cancer field defect. Preferably, the target loci comprise sequences selected from the group consisting of SEQ ID Nos:1-6. Preferably, the target loci are amplified using at least one set of primers in FIG. **12**.

In another embodiment, the quantitation of methylation comprises analyzing whether the SPAG4 regions are hypermethylated or EXT1 regions are hypomethylated as a positive correlation to prostate cancer field defect. Preferably, the target loci comprise sequences selected from the group consisting of SEQ ID Nos:18 and 39. Preferably, the target loci are amplified using at least one set of primers in FIG. **25**.

In another embodiment, the quantitation of methylation comprises analyzing whether the CAV1, EVX1, MCF2L or SPAG4 regions are hypermethylated or FGF1, WNT2, NCR2 or EXT1 regions are hypomethylated as a positive correlation to prostate cancer field defect. Preferably, the target loci comprise sequences selected from the group consisting of SEQ ID Nos:1-6, 18 and 39. Preferably, the target loci are amplified using at least one set of primers in FIGS. **12** and **25**.

In another embodiment, the human subject is a prostate cancer patient.

In another embodiment, the invention is a method of diagnosing high grade prostate cancer field defect in a human subject comprising the steps of: (a) obtaining genomic DNA from the human subject; and (b) quantitating the methylation in at least one target region selected from the group consisting of NCR2 and WNT2 target, wherein significant methylation changes indicate the presence of high grade prostate cancer field defect or prostate cancer, wherein the change is relative to tissue from a second human subject who does not have prostate cancer; and (c) treating the human subject for high grade prostate cancer field defect based the results of steps (a) and (b).

In another embodiment, the invention is a method of screening biomarkers for prostate cancer comprising the steps of: (a) obtaining genomic DNA from a human subject; and (b) quantitating the methylation in at least one target region selected from the group consisting of SEQ ID NOs: 1-6 and 18, 39; wherein significant methylation changes indicate the presence of prostate cancer field defect or prostate cancer, wherein the change is relative to tissue from a second human subject who does not have prostate cancer.

In another embodiment, the invention is a method of screening biomarkers for prostate cancer comprising the steps of (a) obtaining genomic DNA from a human subject; and (b) quantitating the methylation in at least one target region selected from the group consisting of SEQ ID NOs: 61-77 and 94-97; wherein significant methylation changes indicate the presence of prostate cancer field defect or prostate cancer, wherein the change is relative to tissue from a second human subject who does not have prostate cancer.

Other objects, advantages and features of the present invention will become apparent from the following specification taken in conjunction with the accompanying drawings.

BRIEF DESCRIPTION OF DRAWINGS

The invention will be better understood and features, aspects and advantages other than those set forth above will become apparent when consideration is given to the following detailed description thereof. Such detailed description makes reference to the following drawings, wherein:

FIG. **1** shows the sequence of the target region for CAV1 (SEQ ID NO:1).

FIG. **2** shows the sequence of the target region for EVX1 (SEQ ID NO:2).

FIG. **3** shows the sequence of the target region for MCF2L (SEQ ID NO:3).

FIG. **4** shows the sequence of the target region for FGF1 (SEQ ID NO:4).

FIG. **5** shows the sequence of the target region for NCR2 (SEQ ID NO:5).

FIG. **6** shows the sequence of the target region for WNT2 (SEQ ID NO:6).

FIG. **7** shows probe sequences used in the methylation array for the genes CAV1, EVX1, MCF2L, FGF1, NCR2 and WNT2.

FIG. **8** is a diagram demonstrating microdissection of prostate tissue.

FIG. **9**A shows genome-wide distribution of DNA methylation array differences at 385,000 loci in histologically normal tumor-associated (TA) prostate tissues compared to non-tumor associated (NTA) tissues. Significant differences in methylation between TA and NTA prostate tissues were generated using a cut-off of probe score of −log 10 [p] that ranged from 2 to 10 resulting in around 1,000 probes on each chromosome and 18,101 probes in total. After statistical analysis comparing the $\log_2$-ratios between the NTA and TA groups, significant methylation differences between groups were determined using a t-test ($P<0.05$). A total of 615 probes were differentially methylated in TA tissues with 537 demonstrating hypomethylation and 78 hypermethylation. The percentage (axis) is the significantly altered probe number versus the total probe number analyzed for each chromosome. Chromosomes 15 and 20 were differentially methylated to a greater extent than other chromosomes.

FIG. **9**B shows the significant methylation changes across 41,522,036-4,2004,151 on chromosome 15p. The data are represented as a ratio of Mean TA/NTA.

FIG. **9**C shows the significant methylation changes across 33,343,402-33,565,080 on chromosome 20p. The data are represented as ratio of Mean TA/NTA.

FIG. **9**D is a heat map of significant DNA methylation array changes using unsupervised hierarchical clustering. Using more stringent criteria (t-test, $p<0.01$), 87 probes are shown comparing sets of NTA (left) to TA (right) and hierarchically ordered from top to bottom by relatively hypermethylation to hypomethylation. Green indicates relative hypomethylation whereas the red shaded areas demonstrate hypermethylation. The heat map was generated with JAVA TMEV™ (MultiExperiment View).

FIG. **10** is a schematic representation of CpGs analyzed by Pyrosequencing. The ratio of ObsCpG/ExpCpG and GC percentage for all regions are: CAV1 1.2, 60%; EVX1 0.8, 60%; FGF1 1.0, 50%; MCF2L 1.0, 60%; NCR2 0.5, 50%; WNT2 1.0, 50%.

FIG. **11**A-D shows CAV1, EVX1, MCF2L and FGF1 methylations. To analyze CAV1 methylation, we analyzed methylation of ten CpGs and eight out of the ten CpGs showed significantly increased methylation in T (tumor), TAA (tumor-associated adjacent) and TAD (tumor-associated distant) prostate tissue compared to NTA (non-tumor-associated normal prostate tissue). The figure shows methylation percentages of the sixth CpG and they are 14%, 45%, 27% and 26% for NTA, T, TAA and TAD prostate tissues, respectively. *t-test. $P<0.05$ was used for all figures below. To analyze EVX1 methylation, we tested six CpGs for EVX1 and four out of the six showed significantly increased methylation in T, TAA and TAD compared to NTA prostate tissues. This figure shows methylation percentage of the third CpG and they are 22%, 45%, 31% and 28% for NTA, T, TAA and TAD prostate tissues, respectively. For MCF2L, the region detected contains nine CpGs and three out of the nine CpGs showed significantly increased methylation in T, TAA and TAD compared to NTA prostate tissue. This figure shows the methylation for the first CpG and they are 80%, 88%, 85% and 85% for NTA, T, TAA and TAD prostate tissues, respectively. For FGF1, all four CpGs we analyzed showed significantly decreased methylation in TAA and TAD compared to NTA prostate tissue, but no significant change in T prostate tissue. This figure shows methylation percentage of the third CpG and they are 71%, 73%, 60% and 61% for NTA, T, TAA and TAD prostate tissues, respectively.

FIG. **11**E-F shows NCR2 and WNT2 methylations. For NCR2, three CpGs were analyzed within the target region. In the prostate with high grade (Gleason grade ≥8, H) the third CpG showed significantly decreased methylation in T and TAA prostate compared to NTA prostate tissue. However, in the prostate with intermediate grade (Gleason grade 6 & 7, Int), the methylation change of this CpG was only significant in T prostate. This figure shows methylation of the third CpG and they are 75%, 69%, 63%, 68% and 70% for NTA, T (Int), T (H), TAA(H) and TAD(H), respectively. For WNT2, we detected methylation of four CpGs. In the prostate with high grade, two of them showed significantly decreased methylation in all T, TAA and TAD prostate tissues compared to NTA prostate tissue. However, in the prostate with intermediate grade, methylation change was only significant in T prostate tissue. This figure shows methylation of the first CpG and they are 95%, 87%, 79%, 89% and 89% for NTA, T (Int), T (H), TAA (H) and TAD (H), respectively.

FIG. **12** shows the sequences of primers used for pyrosequencing.

FIG. **13** shows AMACR expression in NTA, T, TAA and TAD prostate tissues which will be used in quantitative methylation Pyrosequencing. AMACR expression was assayed with quantitative RT-PCR, the data are shown as ΔCT. Two NTA and three TA (T,TAA,TAD) specimens were excluded from experiential group due to higher AMACR expression.

FIG. **14** shows the sequence of the expanded region of CAV1 to screen for methylation changes associated with PCa.

FIG. 15 shows the sequence of the expanded region of EVX1 to screen for methylation changes associated with PCa.

FIG. 16 shows the sequence of the expanded region of MCF2L to screen for methylation changes associated with PCa.

FIG. 17 shows the sequence of the expanded region of FGF1 to screen for methylation changes associated with PCa. Since there is no CPG island within the promoter region, all the regions shown are within introns between exons one and three.

FIG. 18 shows the sequence of the expanded region of NCR2 to screen for methylation changes associated with PCa.

FIG. 19 shows the sequence of the expanded region of WNT2 to screen for methylation changes associated with PCa.

FIG. 20 shows the sequence of the target region for EXT1 (SEQ ID NO:18).

FIG. 21 shows the sequence of the target region for SPAG4 (SEQ ID NO:39).

FIG. 22 shows probe sequences used in the methylation array for the genes EXT1 and SPAG4 (SEQ ID NOs:86-87).

FIG. 23 is a schematic representation of CpGs analyzed by Pyrosequencing. The ratio of ObsCpG/ExpCpG and GC percentage for all regions are: EXT1 0.8, 60%; SPAG4 0.55, 60%.

FIGS. 24A and 24B show EXT1 and SPAG4 methylations. To analyze EXT1 methylation, we analyzed methylation of six CpGs and four out of the six CpGs showed significantly increased methylation in T (tumor), TAA (tumor-associated adjacent) and TAD (tumor-associated distant) prostate tissue compared to NTA (non-tumor-associated normal prostate tissue). The figure shows methylation percentages of all six CpGs. *t-test. P<0.05 was used for all figures below. To analyze SPAG4 methylation, we tested five CpGs for SPAG4 and five out of the five showed significantly increased methylation in T, TAA and TAD compared to NTA prostate tissues. These figures show methylation percentage of the all five CpGs.

FIG. 25 shows the sequences of primers used for target amplification and pyrosequencing (SEQ ID NOs:88-93).

FIG. 26 shows the sequence of the expanded region of EXT1 to screen for methylation changes associated with PCa (SEQ ID NO:94).

FIG. 27 shows the sequence of the expanded region of SPAG4 to screen for methylation changes associated with PCa (SEQ ID NOs:95-97).

FIGS. 28A, 28B, 28C and 28D show methylation of the EVX1, CAV1, FGF1 and NCR2 in urine from the patients with positive or negative biopsies for prostate cancer.

FIG. 29 shows DNA isolation from paraffin-embedded prostate biopsies.

DESCRIPTION OF THE PRESENT INVENTION

In General

Like other human cancers, prostate cancer development and progression is driven by the interplay of genetic and epigenetic changes (Schulz et al., (2009) *Semin Cancer Biol* 19, 172-180). Changes in somatic DNA methylation constitute a superb source of cancer biomarkers for several reasons. These changes can be detected using PCR methods at single-copy sensitivity and small DNA fragments are more stable in blood and body fluids than RNA or protein species. In addition, acquired DNA methylation differences have been reported for nearly every human cancer. Finally, somatic hypermethylation of CpG island sequences may be more consistent for a given cancer than genetic changes (Nelson et al., (2009) *Endocrinology* 150, 3991-4002). Patterns of DNA methylation in tumors may also discriminate aggressive vs. nonaggressive disease and predict responsiveness to specific treatments (Nelson et al., (2009) *Endocrinology* 150, 3991-4002).

Genetic and epigenetic alterations do not appear to be limited to the cancerous cells, as recent data indicates tissue adjacent or distant to the tumor is also abnormal (Norm et al., (2009) *Prostate* 69, 1470-1479). This field defect (also termed field effect) has been identified in colon and head and neck cancer, as well as prostate based on alterations in gene expression (YP, Y. (2004) *Journal of Clinical Oncology* 22; Chandran et al., (2005) *BMC Cancer* 5, 45) and genomic loss of imprinting (Agnieszka et al., (2009) *International Journal Of Oncology* 35, 87-96). Aberrant methylation patterns in the GSTP1, RARb2, APC and RASSF1A promoters have been detected in normal epithelial or stromal tissue adjacent to cancer (Aitchison et al., (2007) *Prostate* 67, 638-644; Hanson et al., (2006) *J. Natl. Cancer Inst.* 98, 255-261; Henrique et al., (2006) *Mol Cancer Res* 4, 1-8). These genes are altered in the tumor and represent a single gene approach to analyzing the field effect. Results vary as to whether this field effect is limited to the tissue adjacent to the tumor or whether it is found in distant 'normal' tissue.

By use of the present invention, one can reassure men who have a negative biopsy that no cancer is present by testing for the presence of the field defect without additional future biopsies and avoid the complications directly associated with increasing the biopsy number and frequency. If methylation changes associated with a biopsy field defect are detected, more detailed imaging with an MRI and endorectal probe and a more aggressive detection strategy requiring anesthesia and 30-50 biopsies will typically be undertaken to detect and/or characterize the disease. This approach is associated with additional risks associated with anesthesia, infection, bleeding and others, and is not performed routinely. In addition, it is likely these patients would be monitored much more closely.

In developing the present invention, the inventors have analyzed histologically normal tissues from men with and without prostate cancer utilizing a high-throughput technique that simultaneously scans 385,000 regions of the genome. Using a human ENCODE methylation array (Roche Nimblegen), the inventors have found distinct alterations in methylation at specific loci or "target regions". The inventors associated methylation changes at these loci with the presence of prostate cancer. Analysis of these loci in tissue samples from patients will enhance the detection of prostate cancer.

By "histologically normal", we mean prostate tissue that has no evidence of disease in the specimen itself, based on standard morphologic and histochemical criteria used by pathology. By "normal" or "non-tumor associated (NTA)", we mean prostate specimen which not only does not contain cancer itself, as defined by a pathologist, but also does not contain cancer elsewhere in the prostate. By "tumor associated (TA)", we mean a prostate specimen which does not show evidence of cancer, but is taken from a prostate with evidence of cancer in another location. One would appreciate that both "non-tumor associated" and "tumor associated" prostate specimens in this application are "histologically normal" prostate specimens.

Standard PCR methods generally entail amplification of a target region using a pair of forward and reverse primers that are designed to be complementary to sequences flanking the target region. The size of a fragment that can be amplified using PCR can range from less than 50 base pairs (bp) to greater than 10,000 base pairs. Similarly, sequencing of a target region can be accomplished by designing sequencing primers that are complimentary to a sequence less than 50 bp upstream of the target gene or more than 1000 bp upstream depending on the sequencing technology selected. Therefore it is possible to design many permutations of sequencing primers or PCR primer sets that are capable of amplifying a given target region. For example, given a sample containing genomic DNA comprising a 500 bp target gene or region, a primer set can be designed to amplify i) the explicit target region; or ii) a region encompassing the target region including upstream and downstream sequence. If the minimum requirement is a 20 bp primer and the amplified fragment size can range from 500 to 10,000 bp, the number of potential primer sets that can be used to amplify the target region is on the order of 10^4.

This invention discloses a number of preferred primers for amplification of specific target regions. However, one skilled in the art will appreciate that the target regions disclosed in the present invention can be amplified by other than the described primers, which have been presented for purposes of illustration. A number of PCR amplification and sequencing schemes are contemplated and therefore, the scope of the appended claims should not be limited to the description of the embodiments contained herein.

Biomarker Candidates

The inventors identified eight biomarker candidates associated with the genes CAV1, EVX1, MCF2L, FGF1, WNT2, NCR2, EXT1 and SPAG4 which showed significant changes ($p<0.05$) in methylation in target regions when normal and tumor-associated tissues are compared (Table 1). The CAV1, EVX1, MCF2L and SPAG4 regions showed hypermethylation, and the FGF1, WNT2, NCR2 and EXT1 regions showed hypomethylation.

TABLE 1

Gene	Location	Function	Fold Change Microarray	Pyrosequencing
CAV1	7q31.1	Tumor suppressor gene candidate A negative regulator of the Ras-p42/44 MAP kinase cascade Negative regulation of JAK-STAT cascade A scaffolding protein within caveolar membranes	7.6	30% increased in tumor, 12% in tumor-associated, adjacent and distant
EVX1	7p15-p14	Sequence-specific DNA binding, transcription factor A role in the specification of neuronal cell types.	7.1	23% increased in tumor, 6-13% in tumor-associate, adjacent and distant
FGF1	5q31	Fibroblast growth factor receptor signaling pathway Positive regulation of epithelial cell proliferation Embryonic development, cell growth, tumor growth and invasion	0.77	11-15% decreased in tumor-associated, adjacent and distant
MCF2L	13q34	Rho guanine nucleotide exchange factor activity	4.5	8% increased in tumor, 5% in tumor-associated, adjacent and distant
NCR2	6p21.1	Increases efficiency of activated NK cells To mediate tumor cell lysis	0.6	11% decreased in tumor, adjacent and distant for high grade 5% decreased in tumor for intermediate grade
WNT2	7q31.2	Wnt receptor signaling pathway, calcium modulating pathway Implicated in oncogenesis and in several developmental processes (embryogenesis)	0.7	16% decreased in tumor, 5% in adjacent and distant for high grade 8% decreased in tumor for intermediate grade
EXT1	8q24.11	exostosin glycosyltransferase It is a putative tumor suppressor protein, involved in glycosaminoglycan biosynthesis, signal transduction, negative regulation of cell cycle, as well as skeletal development.	0.6	5% decreased in tumor, adjacent and distant histologically normal prostate tissue.
SPAG4	20q11.21	sperm associated antigen 4 Structural molecule activity, Spermatogenesis.	2.1	9% increased in tumor, 8% in adjacent and 12% distant histologically normal prostate tissue

By "gene loci" or "target region", we mean the gene regions described in FIGS. **1-6** and **20-21**. These are the gene regions in which we correlated either hypermethylation or hypomethylation with a prostate cancer field defect. FIG. **12** describes preferred primer sequences for determining methylation perturbations in these selected target regions. FIGS. **12** and **25** describes preferred primer sequences for determining methylation perturbations in these selected target regions.

In a second embodiment, by "gene loci" or "target region", we mean the gene regions described in FIGS. **20-21**. These are the gene regions in which we correlated either hypermethylation or hypomethylation with a prostate cancer field defect. FIG. **25** describes preferred primer sequences for determining methylation perturbations in these selected target regions.

EMBODIMENTS OF THE PRESENT INVENTION

In one embodiment, one can diagnose and/or treat prostate cancer in a human subject by detecting a prostate cancer field defect in histologically normal tissue biopsy specimens taken from men who may have prostate cancer. Based on the results of the detection methods described herein, the subject may be diagnosed with prostate cancer and/or treated for prostate cancer via conventional therapies. It is an advantage of the present invention that fewer biopsies are needed for the detection of prostate cancer. In a preferred embodiment, the presence of prostate cancer field defect can be detected based on only 1-2 core biopsy specimens taken from anywhere in the prostate. Preferably, one would examine one, two, three, four, five, six, seven or eight targets disclosed in Table 1. In addition, in individuals who have had a negative biopsy but whose PSAs continue to rise, analysis of the previously obtained specimens for methylation status in the target regions will direct whether additional evaluation needs to be performed. For example, if the methylation status in any of the target regions is abnormal, a more intensive biopsy set requiring anesthesia would be performed. If not, the patient can be reassured.

In one typical embodiment, prostate tissue samples are obtained via standard transrectal ultrasound and biopsy protocols using an 18 gauge needle (Brooks et al. (2010) *J. Natl. Med. Assoc.* 102(5), 423-429). In another embodiment, prostate tissues are obtained from paraffin blocks of prostate biopsy samples that have already been obtained and examined.

To examine the methylation status of the target regions, one would typically wish to obtain genomic DNA from the tissue samples. The purified genomic DNA is then typically subject to sodium bisulfite modification. We present data demonstrating the ability to obtain enough DNA for analysis using prostate tissue either fresh or paraffin-embedded (See FIG. **29**).

In general, bisulfite modified DNA is subjected to PCR reaction containing a single or multiple pair(s) of primers and probes at specific gene loci of at least one of the CAV1, EVX1, MCF2L, FGF1, WNT2, NCR2, EXT1 and SPAG4 loci detailed in FIGS. **1-6** and **20-21**. The DNA amplification and methylation quantification will be evaluated in one or multiple tubes included as part of a kit. In one embodiment, one would then subject the bisulfite DNA to Methylation-Specific-Quantitative PCR (MS-QPCR) such as MethyLight (WO 00/70090) or HeavyMethyl WO 02/072880). A typical kit for the Mehtylight assay of this embodiment would contain primers and probes of target regions detailed in FIGS. **1-6**, and **20-21**, and wild type reference gene primers such as Beta-Actin, PCR buffer, dNTP, $MgCl_2$, polymerase, positive and negative methylation controls and a dilution reference. In another embodiment, the present invention is the amplification product described above. In a typical embodiment, the DNA targets are bisulfate-modified DNA. In another typical embodiment, the amplification product comprises the amplification product of 2, 3, 4, 5, 6, 7, or 8 of the targets combined in a vessel, such as a tube or well. Preferably, the DNA amplification product is at least 90% target DNA, most preferably 95% or 99%.

In another embodiment, the present invention is a combination of the bisulfite-treated DNA described above and materials useful to determine methylation status.

In another embodiment, one would subject the bisulfite DNA to PCR amplification to amplify at least one of the target regions detailed in FIGS. **1-6** and **20-21**. The PCR products would be subject to pyrosequencing for detection of methylation. The kit for this assay would contain at least one pair of primers for target regions detailed in FIGS. **1-6** and **20-21**, either forward or reverse primer is biotinylated, PCR buffer, dNTPs, $MgCl_2$, Taq polymerase for bisulfite DNA amplification. A sequencing primer and controls, which typically include positive and negative methylation controls and a dilution reference are typically also included.

In another embodiment, bisulfite treated DNA (initial PCR amplification is needed if bisulfited DNA is less than 20 ng) is subjected to an Invader® assay to detect changes in methylation. The Invader® assay entails the use of Invader® chemistry (Hologic Inc.; invaderchemistry.com; Day, S., and Mast, A. Invader assay, 2004; Chapter in Encyclopedia of Diagnostic Genomics and Proteomics. Marcel Dekker, Inc., U.S. Pat. Nos. 7,011,944; 6,913,881; 6,875,572 and 6,872,816). In the Invader® assay, one would use a structure-specific flap endonuclease (FEN) to cleave a three-dimensional complex formed by hybridization of C/T specific overlapping oligonucleotides to target DNA containing a CG site.

The kit for this assay would typically contain the primers and probes of single or multiple target regions detailed in FIGS. **1-6** and **20-21**, and controls, which typically include a reference gene such as Beta-Actin, positive and negative methylation controls and a dilution reference.

In another embodiment, the PCR products are purified, denatured to single-strand and annealed to a sequencing primer for methylation quantification by pyrosequencing at the specific gene loci of at least one of the loci described above.

In all embodiments, one would examine the amplification products for a significant change in methylation pattern. One may examine several criteria to evaluate significant change. For example, a finding of ±50% of the fold-change listed in Table 1 in methylation values of at least one gene loci at one site selected from the group consisting of CAV1, EVX1, MCF2L, FGF1, WNT2, NCR2, EXT1 and SPAG4 would indicate the presence of a prostate cancer field effect. Significant change can also be any statistically meaningful change in methylation pattern relative to normal tissue from men with no history of prostate cancer. For example, significant change may be characterized by a p value less than 0.05. As described below, one may wish to use pyrosequencing as a quantitation method and evaluate the sample for the pyrosequencing percentage, as indicated in Table 1.

One may also wish to examine the change in methylation at specific CpG islands. (The Example below discloses specific characterization of CpG islands for the eight target regions.) Preferably, one would determine the methylation status of two, three, four, five, six, seven or eight of the gene loci detailed in FIGS. **1-6** and **20-21**.

As described above, there are many techniques for measuring DNA methylation. For example, one can use Methylation-Specific-Quantitative PCR (MS-QPCR) or to measure DNA Methylation. (See: Eads C. A., MethyLight: a high-throughput assay to measure DNA methylation. *Nucleic Acids Res.* 2000 Apr. 15; 28(8):E32; 2. Darst R. P., Bisulfite sequencing of DNA. *Curr Protoc Mol Biol.* 2010 July; Chapter 7: Unit 7.9.1-17, and Cottrell S. E., et al., A real-time PCR assay for DNA-methylation using methylation specific blockers, *Nucleic Acids Res.* 2004; 32(1): e10.).

The Examples focus on a preferred method, but one of skill in the art would understand that other methods would be suitable. One simply needs to evaluate the methylation status of CpG islands within the target regions. Examples 1 and 2 below disclose methylation changes at specific CG rich regions, and we anticipate seeing similar changes in adjacent CpG islands not necessarily measured in Examples 1 and 2. Any change in CpG island methylation at one or multiple CG dinucleotides within this island, is considered a positive marker for prostate cancer field defect. One may wish to start with the expanded regions disclosed in Example 3 below.

Preferably, one primer within each set of primers is biotinylated, and the biotinylated PCR products are purified, or captured, with Streptavidin sepharose beads. In a preferred embodiment, one would use the primers detailed in FIGS. **12-25**.

Preferably, the methylation is quantified with PyroMark™MD Pyrosequencing System (Qiagen) using Pyro-PyroMark® Gold Q96 Reagents (Qiagen, Cat#972804) (QIAGEN PyroMark Gold Q96 Reagents Handbook 08/2009, (36-38)). Other approaches for methylation quantification include, for example, methylation specific QPCR or quantitative bisulfite sequencing of methylation.

It is an advantage of the present invention that markers for prostate cancer can be detected noninvasively in bodily fluids, such as urine or semen. The bodily fluid screening method currently used is based on PSA levels in serum and has very poor specificity. Biopsies are more specific, but can produce significant clinical complications, including infection, bleeding and urinary retention. Therefore, in one preferred embodiment of the present invention, the methylation status of the target regions is determined from a urine sample.

In another embodiment, the present invention is a method of identifying biomarkers whose DNA methylation changes associate with high grade PCa, using the protocol described above and in the Examples below. By "high grade", we mean PCa with a Gleason Score 8-10 and a tumor volume of 25-80%. For example, a finding of ±50% of the fold-change in methylation values of at least one gene loci selected from WNT2 and NCR2 would indicate the presence of a high grade PCa field effect. Additional biomarkers for high grade PCa may be identified using the protocol described above and in the Examples below and may also be included in kits.

Generally, patient urine can be obtained, spun and the cell pellet utilized for DNA extraction using protocols as published (Yoshida et al., *International Journal of Cancer*, n/a-n/a; Mehrotra et al., (2008) *Prostate* 68, 152-160). One may wish to use DNA methylation urine-based screen for PCa disclosed below in Example 4. One would then analyze the genomic DNA samples as described above for solid tissue samples. Presence of methylation changes correlating to field effect diagnosis would be analyzed in the same manner as described above.

Generally, when pyrosequencing primers (such as the preferred primers in FIG. **12**) are used, significant methylation changes of at least one of the eight target regions would indicate a prostate cancer field defect. In various embodiments, significant change is indicated by a value of at least ±50% of the pyrosequencing percentages shown in Table 1 or ±50% of the fold-level change in Table 1 or a $p<0.05$ change in specific CpG island methylation patterns.

In a second embodiment, when pyrosequencing primers (such as the preferred primers in FIG. **12** or **25**) are used, significant methylation changes of at least one of the two target regions according to SEQ ID NOs:18 and 39 would indicate a prostate cancer field defect. In various embodiments, significant change is indicated by a value of at least ±50% of the pyrosequencing percentages shown in Table 1 or ±50% of the fold-level change in Table 1 or a $p<0.05$ change in specific CpG island methylation patterns.

In a third embodiment, when pyrosequencing primers (such as the preferred primers in FIG. **12** and/or FIG. **25**) are used, significant methylation changes of at least one of the eight target regions according to SEQ ID NOs:1-6, 18 and 39 would indicate a prostate cancer field defect. In various embodiments, significant change is indicated by a value of at least ±50% of the pyrosequencing percentages shown in Table 1 or ±50% of the fold-level change in Table 1 or a $p<0.05$ change in specific CpG island methylation patterns.

It is another advantage of the present invention that changes in methylation levels of the disclosed markers for prostate cancer can be detected in histologically normal prostate tissue or bodily fluid from men with no history of prostate cancer.

Yet another embodiment of the invention recognizes that the markers can also be used to monitor changes to the prostate as a result of future drug treatments that modify methylation or to assess the clinical severity of an at-risk or cancer patient.

In another embodiment of the present invention, one may wish to use evaluation of methylation status of at least one of the eight target regions for the diagnosis of other cancers, such as breast or colon cancer.

In another embodiment, the present invention is a method of amplifying on of the eight target DNA sequences comprising

(a) providing a reaction mixture comprising a double-stranded bisulfite converted target DNA and (i) at least one pair of primers selected from the group designed to amplify at least one gene selected from the group consisting of CAV1, EVX1, MCF2L, FGF1, WNT2, NCR2, EXT1 and SPAG4, wherein the primer pair comprises a first and a second primer that are complementary to the target DNA sequence, (ii) a polymerase and (iii) a plurality of free nucleotides comprising adenine, thymine, cytosine and guanine; (iv) PCR reaction buffer; (v) $MgCl_2$

(b) heating the reaction mixture to a first predetermined temperature for a first predetermined time to separate the strands of the target DNA from each other;

(c) cooling the reaction mixture to a second predetermined temperature for a second predetermined time under conditions to allow the first and second primers to hybridize with their complementary sequences on the target DNA and to allow the polymerase to extend the primers; and

(d) Repeating steps (b) and (c) at least 10 times.

In one embodiment, the primers are methylated. In another embodiment, the primers are not methylated. In one embodiment, one would use a primer pair designed to amplify one target. In another embodiment, one would use primer pairs designed to amplify 2, 3, 4, 5, 6, 7, or 8 target regions.

Kit Claims

In another embodiment, the present invention is a kit designed for PCa field defect detection. Typically, the kit comprises at least a set of primers, wherein the primers preferably comprise forward and reverse primers designed to amplify a target region selected from the group consisting of CAV1, EVX1, MCF2L, FGF1, NCR2, WNT2, EXT1 and SPAG4 target (SEQ ID NOs: 1-6, 18 and 39), or selected from the group consisting of SEQ ID NOs: 61-77 and 94-97, and other components essential for DNA amplification, preferably, polymerase, dNTP, buffer and a magnesium salt which can release Mg^{2+}. Typically, one can use $MgCl_2$ or $MgSO_4$. In other embodiments, the kit comprises primers designed to amplify two, three, four, five, six, seven or eight targets.

In one embodiment, the primers preferably comprise a forward primer selected from the group consisting of SEQ ID NOs:43, 46, 49, 52, 55 and 58, and a reverse primer selected from the group consisting of SEQ ID NOs:44, 47, 50, 53, 56 and 59, and other components essential for DNA amplification, preferably, polymerase, dNTP, buffer and a Magnesium salt which can release Mg^{2+}. Typically, one can use $MgCl_2$ or $MgSO_4$.

In a second embodiment, the aforementioned kit comprises an alternative set of primers, wherein the primers preferably comprise a forward primer selected from the group consisting of SEQ ID NOs:88 and 91, and a reverse primer selected from the group consisting of SEQ ID NOs:89 and 92.

In a third embodiment, the aforementioned kit comprises a combined set of primers, wherein the primers preferably comprise a forward primer selected from the group consisting of SEQ ID NOs: 43, 46, 49, 52, 55, 58, 88 and 91, and a reverse primer selected from the group consisting of SEQ ID NOs: 44, 47, 50, 53, 56, 59, 89 and 92.

In one preferred embodiment, the kit further comprises FAM or Hex fluorophore-labled methylation and unmethylation-specific probes and is suitable for a closed tube assay for MS-QPCR. In another preferred embodiment, the kit further comprises sequencing primers and is suitable for bisulfite pyrosequencing-based assay. Preferably, the sequencing primers are selected from the group consisting of SEQ ID NOs:45, 48, 51, 54, 57 and 60. Even more preferably, the kit further comprises Streptavidin sepharose beads, enzyme mixture, substrate mixture and dinucleotides.

In a second preferred embodiment, the kit further comprises sequencing primers selected from the group consisting of SEQ ID NOs: 90 and 93.

In a third preferred embodiment, the kit further comprises sequencing primers selected from the group consisting of SEQ ID NOs: 45, 48, 51, 54, 57, 60, 90 and 93.

In another embodiment, the kit comprises components for an Invader® assay to detect changes in methylation. The Invader® assay entails the use of Invader® chemistry (Hologic Inc.) which is composed of two simultaneous isothermal reactions. A primary reaction specifically and accurately detects single-base pair changes measuring methylation. A second reaction is used for signal amplification and result readout.

EXAMPLES

Example 1

Prostate cancer (PCa) is typically found as a multifocal disease suggesting the potential for molecular defects within the morphologically normal tissue. In Example 1, the inventors compared non-tumor associated (NTA) prostate to histologically indistinguishable tumor-associated (TA) prostate tissues and detected a distinct profile of DNA methylation alterations (0.2%) using genome-wide DNA arrays. Hypomethylation (87%) occurred more frequently than hypermethylation (13%). Analysis of TA tissues adjacent and distant from tumor foci revealed a persistence of this methylation defect. Further evaluation and validation of six loci distinguished TA from NTA patients. Still further evaluation and validation of two additional loci distinguished TA from NTA patients. The inventors found a subset of markers which were solely associated with the presence of high grade disease. These findings demonstrate a widespread methylation defect occurs in the peripheral prostate tissues of men with PCa that may be utilized to identify the presence of the disease.

Introduction

'Field cancerization', 'field effect' or 'field defect' were terms first utilized in head and neck tumors to describe an increased frequency of cancer development found outside the visible boundaries of the primary tumor[1]. These genetically or epigenetically compromised cells in histologically normal appearing tissues have the potential to give rise to not only multifocal tumors, but additional cancers after therapy. Although described in colorectal, bladder and esophageal cancer (Jothy et al. (1996) Field effect of human colon carcinoma on normal mucosa: relevance of carcinoembryonic antigen expression. *Tumour Biol* 17, 7; Takahashi, T., et al. (1998) Clonal and Chronological Genetic Analysis of Multifocal Cancers of the Bladder and Upper Urinary Tract, *Cancer Research* 58, 5835-5841; Miyazato, et al. (1999) Microsatellite instability in double cancers of the esophagus and head and neck, *Diseases of the Esophagus* 12, 132-136; Ushijima, T. (2007) Epigenetic Field for Cancerization, *Journal of Biochemistry and Molecular Biology*, Vol. 40, No. 2, March 2007, pp. 142-150 40, 9), a field effect has not been clearly defined for prostate cancer (PCa). Features suggesting the presence of a field effect in PCa include regional multifocality at diagnosis, as well as the increased incidence with aging (Eastham, J. A., et al. (2007) Prognostic Significance of Location of Positive Margins in Radical Prostatectomy Specimens, *Urology* 70, 965-969). Defining an epigenetic field defect associated with PCa would have important clinical ramifications with regard to recurrence and recent interest in focal ablative therapies (Mouraviev, V., et al. Prostate cancer laterality as a rationale of focal ablative therapy for the treatment of clinically localized prostate cancer, *Cancer* 110, 906-910 (2007)).

PCa development and progression is driven by the interplay of genetic and epigenetic changes (Schulz, W. A. & Hoffmann, M. J. Epigenetic mechanisms in the biology of prostate cancer, *Semin Cancer Biol* 19, 172-180 (2009)). One important epigenetic process is the reversible methylation of cytosine at CpG dinucleotides, a sequence underrepresented in the genome except at CpG islands (Brid, A. DNA methylation patterns and epigenetic memory, *Genes Dev* 16, 16 (2002)). DNA methylation regulates gene expression and participates in the nuclear organization of higher organisms. Alterations in DNA methylation are a hallmark of cancer. Typically, adjacent histologically normal tissues are the standard against which many genomic and epigenetic alterations in cancers are identified. In light of the relevance of a potential field defect to both molecular and clinical studies, little is known regarding its distribution and extent in PCa. In part, this has reflected a limitation of techniques for assessing DNA methylation at specific sequences throughout the genome, as well as a lack of specimens without histological evidence of PCa.

In the Example below, the inventors utilized an immunocapture approach to enrich methylated DNA and combine this with DNA microarrays. During an evaluation of control tissues for genome-wide methylation profiles in cancer, the inventors found marked methylation changes in tumor associated (TA) histologically normal appearing prostate tissues extending across susceptible prostate tissues.

Results

Distinct Patterns of DNA Methylation Define Tumor Associated (TA) and Non-Tumor Associated (NTA) Prostate Tissues

As an initial study of the proper controls for cancer analyses, the inventors undertook an analysis of genome-wide methylation changes in histologically normal prostate tissues from men with cancer and compared those to men without cancer. We utilized 385,000 locus arrays based on the Encyclopedia of DNA Elements (ENCODE) 18 sequence that tiles a series of biologically significant regions in the human genome and includes all chromosomes except chromosomes 3 and 17. DNA was initially prepared from four TA and five NTA prostate specimens, digested with restriction enzymes and enriched for methylated DNA by immunoprecipitation (IP) with an antibody against 5-methylcytidine as described (User's, N.S.P.I.i.N. & Guide: DNA Methylation Analysis). Peripheral zone prostate tissues were utilized for these studies as PCa demonstrates a predilection for this region. We carefully evaluated all NTA specimens to confirm the lack of PCa within the prostate by both H&E staining in three dimensions and α-methylacyl-Coa racemase (AMACR) expression (FIG. **13**). Furthermore, the proportion of epithelium to stroma was similar between tissue groups. After labeling, differential hybridization and scanning, we used a probe score cut-off of $-\log_{10}$ [p] range 2-10 to generate about 1,000 probes for each chromosome and a total of 18,101 probes. We then compared the $\log_2$-ratios at individual probes for TA and NTA tissues to evaluate methylation.

Striking differences in methylation were noted when TA and NTA tissues were compared. With $P<0.05$, 615 loci were identified to be differentially methylated in TA tissues, with 537 (87%) hypomethylated and 78 (13%) hypermethylated (FIG. **9**A). Chromosome 15 demonstrated the greatest number of differentially methylated loci (1.13%) in TA tissues, followed by chromosome 20 (0.9%), 1 (0.57%) and 9 (0.51%). Across genomic regions specific areas demonstrated either hyper- or hypomethylation (FIG. **9**B and FIG. **9**C). Fold changes in methylation for TA vs. NTA prostate specimens ranged from 0.02-7.59 (data not shown).

Using more stringent statistical parameters ($P<0.01$), the inventors identified 87 loci which showed significantly differential methylation in TA prostates. These loci were subject to unsupervised hierarchical clustering using TMEV software to generate a heat map. This global view of methylation profile clearly distinguishes TA from NTA prostate tissues (FIG. **9**D). Among the 87 loci, 69 were hypomethylated and 18 hypermethylated in TA tissues (Table 2). Of these, 49 probes were associated with 38 genes and 38 probes were non-gene related. Accession numbers for these genes are listed in Table 3.

TABLE 2

Location of Differentially Methylated Probes

Chromosome location	Total Probe No.	Tumor-Associated vs Normal: Hypomethylation	Tumor-Associated vs Normal: Hypermethylation
1	5	P14KB (2), NR (3)	
2	3	ACCN4 (1), TRPM8 (1), NR (1)	
4	1		NR (1)
5	5	SEPT8 (2), FGF1 (1), NR (2)	
6	6	NCR2 (3), TFEB (1), NR (2)	
7	7	WINT2 (1), GRM8 (1), NR (1)	EVX1 (1), GRM8 (1) CAV1 (1), NR (1)
8	1	EXT1 (1)	
9	2	IER5L (1), NR (1)	
11	7	NRXN2 (2), NR (5)	
13	6	F7 (1), NR (2)	MCF2L (2), NR (1)
14	3	NR (3)	
15	11	TP53BP1 (1), MAP1A (2), FRMD5 (3), NR (1)	FRMD5 (2), SERF2 (1), NR (1)
16	3	RAB11FIP3 (1), NR (1)	DECR2 (1)
18	5	SERPINB2 (1), NR (3)	SERPINB8 (1)
19	3	LILRA5 (1), LENG12 (1)	CNOT3 (1)
20	8	GDF5 (1), CEP250 (2), ERGIC3 (1), FER1L4 (1), NR (1)	FAM83C (1), SPAG4 (1)
21	7	NR (6)	NR (1)
22	4	DEPDC5 (1), SYN3 (1), PISD (1), NR (1)	
Total	87	69	18

Significant methylated probes between normal and tumor-associated prostate were generated from Methylation array using a cut-off probes score-log10 [p] ranged from 2-10 to generate 18,101 probes in total, and then log2ratio for these probes were compared between TA and NTA, t-test P < 0.01. Sixty-nine probes were hypomethylated, 36 probes related to 27 non-gene regions. NR represents not related to any gene.

TABLE 3

Gene Symbol	Gene Name	Accession #
P14KCB	Phosphatidylinosol 4-kinase, catalytic, beta	NM_002651 (SEQ ID NO: 7)
ACCN4	Amiloride-sensitive cation channel, pituitary	NM_182847 (SEQ ID NO: 8)
TRPM8	Transient receptor potential cation channel, subfamily M, member 8	NM_024080 (SEQ ID NO: 9)
SEPT8	Septin	AF440762 (SEQ ID NO: 10)
FGF1	Fibroblast growth factor 1 (acidic)	NM_000800 (SEQ ID NO: 11)
NCR2	Natural cytotoxicity triggering receptor 2	AJ010100 (SEQ ID NO: 12)
TFEB	Transcription factor EB	NM_007162 (SEQ ID NO: 13)
EVX1	Even-skipped homeobox 1	NM_001989 (SEQ ID NO: 14)
CAV1	Caveolin 1	NG_012051.1 (SEQ ID NO: 15)
WNT2	Wingless-type MMTV integration site family member 2	BC078170 (SEQ ID NO: 16)
GRM8	Glutamate receptor, metabotropic 8	NM_000845 (SEQ ID NO: 17)
EXT1	Exosloses (multiple) 1	BC001174 (SEQ ID NO: 18)
IER5L	Immediate early response 5-like	NM_203434 (SEQ ID NO: 19)
NRXN2	Neurexin 2	NM_138734 (SEQ ID NO: 20)

TABLE 3-continued

Gene Symbol	Gene Name	Accession #
MCF2L	Cell line derived transforming sequence-like	NM_024979 (SEQ ID NO: 21)
F7	Coagulation factor VII	NM_019616 (SEQ ID NO: 22)
TP53BP1	Tumor protein p53 binding protein 1	NM_005657 (SEQ ID NO: 23)
MAP1A	Microtubule-associated protein 1A	NM_002373 (SEQ ID NO: 24)
SERF2	Small EDRK-rich factor 2	BC015491 (SEQ ID NO: 25)
FRMD5	FERM domain containing 5	NM_032892 (SEQ ID NO: 26)
DECR2	2,4-dienoyl CoA reductase 2, peroxisomal	AK128012 (SEQ ID NO: 27)
RAB11FIP3	RAB11 family interacting protein 3 (class III)	NM_014700 (SEQ ID NO: 28)
SERPINB2	Serpin peptidase inhibitor, clade B (ovalbumin), member 2	NM_002575 (SEQ ID NO: 29)
SERPINB8	Serpin peptidase inhibitor, clade B (ovalbumin), member 8	BC034528 (SEQ ID NO: 30)
CNOT3	CCR4-NOT transcription complex, subunit 3	BC016474 (SEQ ID NO: 31)
LILRA5	Leukocyte immunoglobulin-like receptor, subfamily A (with TM domain), member 5	NM_181985 (SEQ ID NO: 32)
LENG12	Leukocyte receptor cluster (LRC) member 12	NM_033206 (SEQ ID NO: 33)
FAM83C	Family with sequence similarity 83, member C	NM_178468 (SEQ ID NO: 34)
GDF5	Growth differentiation factor 5	NM_000557 (SEQ ID NO: 35)
CEP250	Centrosomal protein	AF022655 (SEQ ID NO: 36)
ERGIC3	ERGIC and golgi 3	NM_015966 (SEQ ID NO: 37)
FER1L4	Fer-1-like 4	NR_024377.1 (SEQ ID NO: 38)
SPAG4	Sperm associated antigen	NM_003116 (SEQ ID NO: 39)
PISD	Phosphatetidylserine decarboxylase	CR456540 (SEQ ID NO: 40)
DEPDC5	DEP domain containing 5	AJ698951 (SEQ ID NO: 41)
SYN3	Synapsin III	NM_003490 (SEQ ID NO: 42)

A subset of the 20 genes were chosen for further evaluation, based on genomic location, putative biological function, extent of methylation and primer success in a separate validation using a set of 24 TA and NTA prostate specimens. Quantitative Pyrosequencing was employed to allow a more accurate evaluation of the extent of DNA methylation[11,12]. Internal controls for the adequacy of bisulfite conversion were performed. Six loci, which were associated with the genes CAV1, EVX1, MCF2L, FGF1, NCR2 and WNT2, showed significant methylation changes ($P<0.05$). The three loci associated with CAV1, EVX and MCF2L were hypermethylated and the three loci associated with FGF1, NCR2 and WNT2 were hypomethylated. The location of the probes and CG's assessed by Quantitative Pyrosequencing are shown in FIGS. **10** and **12**. The six loci in pyrosequencing are close or overlap the methylation array regions but sequences are different. The sequences listed in FIG. **1-6** have covered both array region (FIG. **7**) and pyrosequencing regions. These data demonstrate that TA tissues have a methylation profile distinct from men without cancer (NTA) and that these changes alter specific regions of the genome.

Identification of a Widespread Methylation Field Defect in the Peripheral Prostate.

Preferential alteration in tissues adjacent to PCa tumor foci, i.e., field defect, suggests a peritumoral response. To evaluate whether tissues adjacent to PCa tumor foci are preferentially altered, the extent of field defect was assessed in 26 additional histologically normal tissues by looking at the methylation status of these six differentially methylated markers. The inventors micro-dissected normal tissues adjacent (TAA, 2 mm) and distant (TAD, >10 mm) from the main tumor focus for each of the specimens (FIG. **8**). Histological 3-dimensional H&E staining and AMACR expression determined by qPCR were applied to rule out any contamination by tumor cells or the presence of high grade prostatic intraepithelial neoplasia (HGPIN), a putative cancer precursor (Ayala, A. G. & Ro, J. Y. Prostatic Intraepithelial Neoplasia: Recent Advances, *Archives of Pathology & Laboratory Medicine* 131, 1257-1266 (2007)). Increased AMACR expression was found in 2 NTA and 3 TA tissues that were subsequently excluded from further analysis (FIG. **13**).

When compared to NTA tissues, hypermethylation of probes associated with CAV1, EVX1, MCF2L and hypomethylation of FGF1 demonstrated significant changes in both TAA, as well as TAD tissues (FIG. **11**A-D and Table 4). Notably, there was no difference in the extent of methylation seen at different distances from the tumor when TAA and TAD tissue sets were compared. Significant methylation changes were also seen in tumor samples when compared to NTA tissues for CAV1, EVX1, MCF2L, NCR2 and WNT2, revealing a persistence of these changes in the associated cancer. These data indicate that the epigenetic field defect in the prostate is widespread and not solely localized to the immediate peritumor environment.

TABLE 4

Methylation Percentage Of All Analyzed CpGs For Each Gene

	CAV1			EVX1			MCF2L			FGF1			NCR2[1]			WNT2[1]		
	NTA	TAA	TAD	NTA	TAA	TAD	NTA	TAA	TAD	NTA	TAA	TAD	NTA	TAA	TAD	NTA	TAA	TAD
CG1	4.5	8.8*	9.6*	30.5	38.8*	32.6	80.2	85.2*	85.3*	80.4	70.7*	70.8*	54.3	50.8	52.1	95.4	89.8*	89.8*
CG2	14.6	22.4*	21.3*	28.2	36.9*	29.9	77.0	85.3*	85.1	71.7	60.7*	59.8*	30.5	30.6	30.9	94.9	91.0*	91.5*
CG3	17.8	27.7*	25.8*	22.7	30.8*	27.8*	96.3	97.4	96.5	71.2	60.2*	60.9*	74.7	68.6*	70.7	100	99.5	100
CG4	13.8	24.3*	23.0*	50.4	55.4	48.3	84.8	82.1	80.7	81.1	72.9*	71.1*				99.8	99.5	100
CG5	15.3	25.0*	21.9*	46.5	51.7	47.2	79.9	86.1	87.5									

TABLE 4-continued

	Methylation Percentage Of All Analyzed CpGs For Each Gene																	
	CAV1			EVX1			MCF2L			FGF1			NCR2[1]			WNT2[1]		
	NTA	TAA	TAD	NTA	TAA	TAD	NTA	TAA	TAD	NTA	TAA	TAD	NTA	TAA	TAD	NTA	TAA	TAD
CG6	14.9	27.2*	26.4*	36.7	44.8*	40.6*	75.3	81.0	82.1									
CG7	18.9	28.0*	26.0				89.6	94.3	93.6									
CG8	8.25	15.4*	14.7*				57.8	57.2	55.8									
CG9	15.8	22.7	19.5				39.8	31.4	38.1									
CG10	17.9	26.7*	28.6*															

*P < 0.05

[1]High grade tumor only

Specific Methylation Loci are Associated with a High-Grade PCa Field Defect.

An important issue in PCa is the early identification and treatment of lethal high grade PCa. The inventors Analyzed a subset of TA tissues that were associated with either intermediate or high grade cancer using pyrosequencing. When compared to NTA tissues, an analysis of NCR2 and WNT2 demonstrated significant hypermethylation and hypomethylation, respectively, in TA tissues associated with high-grade specimens (FIG. **11**E-F). This was not seen in TA tissues associated with intermediate grade PCa.

Discussion

Research has theorized that a field defect may underlie the development of multifocal cancers (Slaughter D. P., Southwick H. W., Smejkal, W.; Field cancerization in oral stratified squamous epithelium; Clinical implications of multicentric origin, *Cancer* 6, 6 (1953)). Initial efforts in characterizing this process focused on genetic alterations (Braakhuis, B. J. M., Tabor, M. P., Kummer, J. A., Leemans, C. R. & Brakenhoff, R. H., A Genetic Explanation of Slaughter's Concept of Field Cancerization, *Cancer Research* 63, 1727-1730 (2003); Garcia, S. B., Park, H. S., Novelli, M. & Wright, N. A. Field cancerization, clonality, and epithelial stem cells: the spread of mutated clones in epithelial sheets, *The Journal of Pathology* 187, 61-81 (1999)), but more recently epigenetic changes have been proposed as a etiology (Hu, M., et al. Distinct epigenetic changes in the stromal cells of breast cancers, *Nat Genet* 37, 899-905 (2005); Wolff, E. M., et al., Unique DNA Methylation Patterns Distinguish Noninvasive and Invasive Urothelial Cancers and Establish an Epigenetic Field Defect in Premalignant Tissue, *Cancer Research* 70, 8169-8178). In the present study, we conclusively demonstrate, using unbiased methylation arrays, that significant changes in DNA methylation occur at specific loci within histologically normal tissues associated with PCa. Furthermore, these changes are widespread and not restricted to the immediate peritumor environment. These changes also permit a clear distinction between tumor associated and non-tumor associated prostate tissue.

To date, epigenetic profiling of tumor-associated histologically normal tissues has not been performed in solid tumors. Our genome-wide assessment of specific loci demonstrates that hypomethylation was seen more commonly than hypermethylation in TA prostate tissues. These changes occurred in 0.2% of the 385,000 loci studied. DNA hypomethylation may occur early in solid tumor carcinogenesis based on its identification in precancerous lesions, including prostatic intraepithelial neoplasia (Feinberg, A. P., Ohlsson, R. & Henikoff, S., The epigenetic progenitor origin of human cancer, *Nat Rev Genet* 7, 21-33 (2006); Suzuki, K., et al. Global DNA demethylation in gastrointestinal cancer is age dependent and precedes genomic damage, *Cancer Cell* 9, 199-207 (2006)). This may lead to chromatin instability and contribute to the neoplastic phenotype. Our data extend these findings and suggest that epigenetic alterations may precede even the histologic changes identified with these precursor lesions. These DNA methylation changes may reflect diet and other environmental exposures (Richardson, B. C., Role of DNA Methylation in the Regulation of Cell Function: Autoimmunity, Aging and Cancer, *The Journal of Nutrition* 132, 2401S-2405S (2002); Mathers J C, S. G., Relton C L, Induction of epigenetic alterations by dietary and other environmental factors, *Adv Genet.* 71, 37 (2010)) and represent a potential avenue for prevention.

Epigenetic alterations limited solely to the immediate peritumor environment suggest a response of the surrounding tissue to the primary cancer. Single gene epigenetic studies have identified these changes in a subset of specimens adjacent to the primary PCa (Mehrotra, J., et al., Quantitative, spatial resolution of the epigenetic field effect in prostate cancer, *Prostate* 68, 152-160 (2008); Aitchison, A., Warren, A., Neal, D. & Rabbitts, P. RASSF1A promoter methylation is frequently detected in both pre-malignant and non-malignant microdissected prostatic epithelial tissues, *Prostate* 67, 638-644 (2007); Hanson, J. A., et al., Gene Promoter Methylation in Prostate Tumor-Associated Stromal Cells, *J. Natl. Cancer Inst.* 98, 255-261 (2006); Henrique, R., et al., Epigenetic heterogeneity of high-grade prostatic intraepithelial neoplasia: clues for clonal progression in prostate carcinogenesis, *Mol Cancer Res* 4, 1-8 (2006)). In contrast, in the present epigenomic profiling study, we found that these alterations consistently extended to regions distant from tumor foci. In bladder cancer, a disease also characterized by multifocality and recurrence, there is no dependence on distance from the primary tumor (Wolff, E. M., et al., Unique DNA Methylation Patterns Distinguish Noninvasive and Invasive Urothelial Cancers and Establish an Epigenetic Field Defect in Premalignant Tissue, *Cancer Research* 70, 8169-8178). A similar widespread field defect was demonstrated during evaluation of Insulin-like Growth Factor 2 (IGF2) loss of imprinting in peripheral prostate tissues (Bhusari, S., Yang, B., Kueck, J., Huang, W. & Jarrard, D. F., Insulin-like growth factor-2 (IGF2) loss of imprinting marks a field defect within human prostates containing cancer, *The Prostate,* 2011 Mar. 22). There has been recent interest in the treatment of PCa using focal ablative therapy (Mouraviev, V., et al., Prostate cancer laterality as a rationale of focal ablative therapy for the treatment of clinically localized prostate cancer, *Cancer* 110, 906-910 (2007)). The current findings suggest a field of susceptibility that might be utilized to help select patients who would be poor candidates for this approach.

In the current study, we focused on a high-resolution genome-wide analysis of methylation status rather than on specific gene promoter regions. The ENCODE18 human genome project includes gene-enriched areas thought to be biologically significant, a fact that potentially may generate a bias in our analyses. The majority of probes fell within CpG islands (Saxonov, S., Berg, P. & Brutlag, D. L., A genome-wide analysis of CpG dinucleotides in the human genome distinguishes two distinct classes of promoters, *Proceedings of the National Academy of Sciences of the United States of America* 103, 1412-1417 (2006); Fatemi, M., et al., Footprinting of mammalian promoters: use of a CpG DNA methyltransferase revealing nucleosome positions at a single molecule level, *Nucleic Acids Research* 33, e176), but none fell into defined gene promoter regions. Hypermethylation within promoters has been linked to decreased gene expression (J Y, P., Promoter hypermethylation in prostate cancer, *Cancer Control* 17, 11; Cooper, C. S. & Foster, C. S., Concepts of epigenetics in prostate cancer development, *Br J Cancer* 100, 240-245 (2008)), but the function of CpG islands outside these regions remains uncertain. Given the potential for long-range epigenetic silencing, these changes may herald alterations in gene expression affecting distant regions (Clark, S. J., Action at a distance: Epigenetic silencing of large chromosomal regions in carcinogenesis, *Human Molecular Genetics* 16, R88-R95 (2007)), or, alternatively, reflect altered nuclear structure.

The current findings have several additional implications. PSA-based screening has been widely criticized for its failure to specifically identify lethal PCa (Adami, H.-O., The prostate cancer pseudo-epidemic, *Acta Oncologica* 49, 298-304). This study raises the possibility of using a tissue test, or potentially urine-based test, for the detection of disease (and specifically high-grade disease) based on abnormalities found in not only the tumor but in the associated TA tissues. This would be expected to demonstrate increased sensitivity by increasing the percentage of affected cells able to be detected. In addition, the assessment of alterations that occur in PCa have typically compared tumor to 'normal' tissues within the same prostate gland. The current study indicates that the histologically normal tissue from men who have PCa already contains methylation abnormalities, which may lead to an underestimation of epigenetic changes that exist in the associated cancers.

Example 2

Material and Methods

Tissue Samples

Samples termed non-tumor associated (NTA, mean 63, age range 55-81 years old) were obtained from organ donation or cystoprostatectomy. The presence of any associated PCa was ruled out by extensive histological evaluation. Tumor-associated (TA, mean 61, age range 57-64 years old) prostate tissues were obtained from patients who underwent radical prostatectomy for PCa (Table 5). This study was approved by the institutional review boards at the University Pittsburgh and the University of Wisconsin-Madison. A separate validation group of 14 NTA (mean 60, age range 55-70 years old) and 12 TA (mean 58, age range 53-64 years old) samples were also assessed.

TABLE 5

Subject clinical and pathological characteristics

	Methylation Array		Pyrosequencing		
	NTA	TA	NTA	TA	T, TAA, TAD
Number	5	4	14	11	26
Age (yr)	63 (55~81)	61 (57~64)	60 (55~70)	59 (51~67)	58 (44~69)
Tumor Volume (%)		6.3		5.1	27.1
Gleason grade					
Intermediate		4		6	16
High					10
Pathological stage					
T2				3	
T2a				1	1
T2b					2
T2c		3		6	14
T3a		1		1	2
T3b					4
PSA (ng/ml)		7.7		5.9	6.9

NTA: non-tumor-associated normal,
TA: tumor-associate,
T: tumor,
TAA: tumor-associated adjacent,
TAD: tumor-associated distant.
Stages for three patients are unavailable.
Intermediate: 3 + 3, 3 + 4;
High: 4 + 4, 4 + 5, 5 + 5.

To define the relationship of methylation to tumor foci, histological sections containing both cancer and normal regions were generated from 26 (mean 58, age range 44-69 years old) radical prostatectomy specimens under the direction of a genitourinary pathologist. Microdissection was performed to obtain tumor (T), normal tissue adjacent (2 mm) to tumor foci (TAA) and at a greater distance (10 mm, TAD) as previously described (FIG. **8**) (Bhusari, S., Yang, B., Kueck, J., Huang, W. & Jarrard, D. F., Insulin-like growth factor-2 (IGF2) loss of imprinting marks a field defect within human prostates containing cancer, *The Prostate,* 2011 Mar. 22). The clinical and pathological characteristics of the PCa study population are presented in Table 5. Of these patients, 16 had an intermediate grade cancer (Gleason score between 6 and 7; tumor volumes 5-70%) and 10 had high grade cancer (Gleason score 8-10; tumor volumes 25-80%). Prostate specimens were confirmed to have no tumor by both H&E staining in three dimensions and AMACR expression. For AMACR analysis, RNA was extracted using an RNeasy Mini Kit (Qiagen, CA), and 300 ng RNA was reverse transcribed with Ominscript® (Qiagen, CA). Quantitative real time PCR for total AMACR was performed using primer sequences as reported[33] (incorporated herein by reference).

DNA Methylation Microarrays

Genomic DNA was isolated using the DNeasy Blood & Tissue kit (Qiagen, CA). DNA used for microarray analysis was additionally incubated with RNaseA for 30 mins at 37° C. to prevent any RNA contamination. Roche NimbleGen ENCODE HG18 DNA methylation arrays were utilized. These arrays contain 385,000 50-75mer oligonucleotides (probes) that cover biologically significant pilot regions of the human genome at 60-bp spacing.

Sample preparation for the microarray was performed following the manufacturer's protocol. Briefly, up to 6 micrograms of high-quality genomic DNA was digested with MseI (New England Biolabs, Ipswich, Mass.) to produce 200-1,000 bp fragments while keeping CpG islands intact, and was then heat denatured to single strand DNA fragments. Methylated DNA fragments were immunoprecipitated (IP) overnight at 4° C. with 1 μg of antibody against 5-methyl cytidine (Abcam, Cambridge, Mass.) and incubated with agarose beads for two hours. The DNA: antibody:bead mixture was digested with Proteinase K overnight at 55° C. before purified with phenol-chloroform. Methylated immunoprecipited (MeDIP) DNA and flowthrough were validated with PCR primers specific for methylated and un-methylated regions as described by Weber et al (Weber, M., et al. Chromosome-wide and promoter-specific analyses identify sites of differential DNA methylation in normal and transformed human cells. Nat Genet 37, 853-862 (2005)). Enriched DNA was amplified with the WGA2 Kit (Promega, Madison, Wis.). The labeling of IP and input DNA, microarray hybridization and scanning were performed by NimbleGen (Reykjavik, Iceland) as described (Roche. NimbleGen Arrays User's Guide DNA Methylation Arrays Version 7.2, (2010). Data were extracted from scanned images using NimbleScan 2.4 extraction software (NimbleGen Systems, Inc.). The samples were assayed in duplicate.

Sodium Bisulfite Modification and Quantitative Pyrosequencing

Sodium bisulfite modification of genomic DNA was carried out using the EpiTect Bisulfite Kit (Qiagen, CA) according to the manufacturer's protocol. Bisulfite modified DNA was then amplified using PCR with either the forward or reverse biotinylated primer in preparation for Pyrosequencing (Jörg Tost, El Abdalaoui, H., and Ivo Glynne Gut., Serial pyrosequencing for quantitative DNA methylation, *BioTechniques,* 40, 6 (2006)). The PCR and sequence primers for Pyrosequencing were designed using PyroMark Assay Design 2.0 (Qiagen), and positioned on or adjacent to the probe sites which showed significant ($p<0.01$) methylation changes. The analyzed regions for specific loci are listed in FIG. **10**, while primer sequences are listed in FIG. **12**. The biotinylated PCR products were captured with Streptavidin sepharose beads, denatured to single strand and then annealed to the sequencing primer for the Pyrosequencing assay. SssI methylase-treated bisulfite-converted DNA from HPEC (human prostate epithelial cell) and PPC1 cells were used as positive controls, and water substituted for DNA was used as a negative control. The methylation was quantified with the PyroMark™MD Pyrosequencing System (Qiagen, CA) within the linear range of the assay. All the samples were analyzed in at least two independent experiments, both in duplicate.

Data Analysis

Scaled $\log_2$-ratio GFF file and P-value GFF file were used for microarray analysis. These were extracted from scanned images provided by Nimblegen (NimbleGen Systems, Inc.). The scaled $\log_2$-ratio data is the ratio of the test sample and input signals co-hybridized to the array. Scaling was performed by subtracting the bi-weight mean for all features of the array. From the scaled $\log_2$-ratio data, a fixed-length window was placed around each consecutive probe and the one-sided Kolmogorov-Smirnov (KS) test was applied to determine whether the probes were drawn from a significantly more positive distribution of intensity log-ratios than those in the rest of array. The resulting score for each probe is the $-\log_{10}$ p-value. The probe IDs were first chosen based on a p-value $-\log_{10}$ [p] that ranged from 2 to 10 resulting in around 1,000 probes on each chromosome and 18,101 probes in total. After statistical analysis comparing the $\log_2$-ratios between the NTA and TA groups, significant methylation differences between groups were determined using t-test ($P<0.05$). Significantly changed probes were clustered by Java MultiExperiment View (MEV 4.6.2) with unsupervised Hierarchical Clustering (Saeed Al, B. N., Braisted J C, Liang W, Sharov V, Howe E A, et al., TM4 microarray software suite, *Methods in Enzymology* 411, 60 (2006)).

For quantitative Pyrosequencing, the methylation at each CpG site was expressed as a percentage. A t-test was used to test for differences between groups, $P<0.05$ was considered statistically significant. The Spearman test was used to determine correlations, with significance set at $P<0.05$; r represents the measure of the relationship between two variables, and varies from −1 to +1.

Example 3

CpG Islands

Based on the teachings of Examples 1 and 2, one can also check the CpG islands that are located in the promoter regions of the genes showing significant methylation changes correlating with PCa, preferably the region within about 5 kb upstream of the transcription start site (TSS), because the methylation of these CpG islands will change the gene expressions and affect gene functions. The inventors' primary research (data not shown) showed that one may wish to start with genes CAV1, EVX1, MCF2L and WNT2. The expanded regions of each of the six genes for preferred screening of methylation changes are detailed in FIGS. **14-19**.

FGF1 and NCR2 do not have CpG islands within the promoter regions. For FGF1, the expanded regions for preferred screening of methylation changes would be 300 bps upstream and 1 kb downstream of the target region reported in Example 1, as well as about 5 Kb upstream of the translation start site ATG (detailed in FIG. **17**). For NCR2 the expanded regions for preferred screening of methylation changes would be the region between exon two and three and the two CpG islands between exon four and five (detailed in FIG. **18**).

Example 4

Development of a DNA Methylation Urine-Based Screen for Lethal PCa

As disclosed in Example 1, specific loci associated with field defect appear to be preferentially altered in lethal, high grade PCa, which is responsible for the majority of PCa deaths. Establishing the role epigenetic changes play in the development of lethal PCa can lead to better diagnosis and treatment of high grade PCa. We envision that epigenetic field defect characterized by changes in DNA methylation in histologically normal appearing cells within the prostate can be utilized to identify patients with lethal disease.

Introduction

In 2010, PCa was the most commonly diagnosed cancer in Wisconsin men (Fu V X, Dobosy J R, Desotelle J A, Almassi N, Ewald J A, Srinivasan R, Berres M, Svaren J, Weindruch R, Jarrard D F., Aging and cancer-related loss of insulin-like growth factor 2 imprinting in the mouse and human prostate, *Cancer Res.* 2008 Aug. 15; 68(16):6797-802), and is the second most common cause of cancer death (after lung cancer), with over 600 men succumbing to the disease (Jemal A, Siegel R, Xu J, Ward E., Cancer statistics, 2010. 1. *CA Cancer J. Clin.* 2010 September; 60(5):277-300). Over 70% of PCa deaths occur in men diagnosed with high grade (Gleason Score 8-10) disease or high volume intermediate grade disease (Gleason Score 6-7), making the detection of these variants at an earlier time point critical (Stephenson A. J., Kattan M. W., Eastham J. A., Bianco F. J., Jr., Yossepowitch O., Vickers A. J., Klein E. A., Wood D. P., Scardino P. T., Prostate cancer-specific mortality after radical prostatectomy for patients treated in the prostate-specific antigen era, *J. Clin. Oncol.* 2009 Sep. 10; 27(26): 4300-5). Low volume (<10%) intermediate and lower grade cancers have a much more indolent natural history. Several striking features of PCa include its multifocality and marked increase in incidence with aging. These characteristics suggest a 'field defect' may be an important component in the etiology of PCa. To date, cancer diagnosis has focused on the finding of cancer cells, typically by biopsy, yet the presence of alterations associated with histologically normal prostate tissue is as yet an untapped resource in both the diagnosis and understanding of the etiology of this disease.

Over 600,000 diagnostic prostate biopsies are performed annually in the United States. The false negative rate is as high as 34%, and roughly 20-35% of patients sent for repeat biopsy are ultimately diagnosed with cancer (Djavan B, Zlotta A, Remzi M, Ghawidel K, Basharkhah A, Schulman C C, Marberger M. Optimal predictors of prostate cancer on repeat prostate biopsy: A prospective study of 1,051 men, *J. Urol.* 2000 April; 163(4):1144-8). Prostate biopsy is associated with risk of bleeding, urinary distress and hospitalization for infection that increases with each subsequent biopsy. Alternatively, patients whose biopsies are initially negative with an elevated PSA represent a serious clinical dilemma, and are at risk for additional evaluation costs and procedures, including saturation biopsy that is performed in the operating room under anesthesia. Men in this situation experience significant anxiety as well (Katz D A, Jarrard D F, McHorney C A, Hillis S L, Wiebe D A, Fryback D G., Health perceptions in patients who undergo screening and workup for prostate cancer, *Urology* 2007 February; 69(2): 215-20). The development of a non-invasive test to augment PSA screening would be of enormous benefit to society.

Currently utilized screening tests (serum prostate specific antigen (PSA) and digital rectal exam have only a modest predictive value (Strope S A, Andriole G L, Prostate cancer screening: Current status and future perspectives, *Nat. Rev. Urol.* 2010 September; 7(9):487-93). PSA isoforms add little specificity. Body fluids including semen and urine may contain molecular information regarding the presence of PCa. PCa and prostate epithelial cells are shed into biologic fluids, particularly when the prostate is subjected to physical manipulation, thus creating the potential for their noninvasive detection in either urine or expressed prostatic fluid. Attempts at detecting PC cells in urine by traditional cytology are thwarted by unacceptably low sensitivities, although specificities were consistently high (Fujita K., Pavlovich C. P., Netto G. J., Konishi Y., Isaacs W. B., Ali S., DeMarco A., Meeker A. K., Specific detection of prostate cancer cells in urine by multiplex immunofluorescence cytology, *Hum. Pathol.* 2009 July; 40(7):924-33). This is due primarily to low numbers of PC cells present in urine cytology preparations. Analyzing cells shed from the abnormal prostate bypasses this important hurdle and represents the first effort of its kind in prostate and many other cancers.

To date, one of the few field defect alterations found in both non-cancerous peripheral prostate tissue and in associated prostate tumors is our finding of a loss in the typical imprint of the IGF2 gene (Fu V. X., Dobosy J. R., Desotelle J. A., Almassi N., Ewald J. A., Srinivasan R., Berres M., Svaren J., Weindruch R., Jarrard D. F., Aging and cancer-related loss of insulin-like growth factor 2 imprinting in the mouse and human prostate, *Cancer Res.* 2008 Aug. 15; 68(16):6797-802). We have demonstrated that this is not a peritumor phenomenon (i.e. adjacent response to the cancer), but is widely prevalent even in distant areas within the peripheral prostate (Bhusari S., Yang B., Kueck J., Huang W., Jarrard D. F., Insulin-like growth factor-2 (IGF2) loss of imprinting marks a field defect within human prostates containing cancer, *Prostate* 2011 Mar. 22). Our lab has expanded these studies to other epigenetic phenomenon and recently using a series of Nimblegen™ ENCODE18 Methylation Arrays, which survey the whole human genome, have identified 87 loci (out of 385,000 loci surveyed) that exhibit altered methylation ($p<0.01$) in the peripheral prostate tissue of men who have the disease when compared to those that do not (FIG. **9**D). Interestingly these methylation defects are found both in gene and relatively gene-free areas of the genome. To date, we have screened 16 of these loci and validated 6 (CAV1, EVX1, MCF2L, FGF1, WNT2 and NCR2) using quantitative bisulfite Pyrosequencing in an additional cohort of 40 patients (FIG. **11**). Notably, we found that methylation at the WNT2 and NCR2 were associated with the field defect in high grade, but not intermediate grade, cancers (FIG. **11**E-F). This striking finding suggests these high grade cancers may have a molecular fingerprint present in the adjacent normal tissues that could assist in the earlier diagnosis of the disease. Finally, analyses of associations between tumor volume, PSA, and the extent of methylation demonstrated a significant association between FGF1 and increased tumor volume ($P=0.036$, $r=0.4616$) (see Example 1). In addition to histological confirmation of the absence of cancer in these prostate tissues, we also performed AMACR expression analysis, a specific marker for the presence of PCa (Ananthanarayanan V., Deaton R. J., Yang X. J., Pins M. R, Gann P. H., Alpha-methylacyl-CoA racemase (AMACR) expression in normal prostatic glands and high-grade prostatic intraepithelial neoplasia (HGPIN): association with diagnosis of prostate cancer, *Prostate* 2005 Jun. 1; 63(4):341-6), to rule out contamination with cancer cells (data not shown). In sum, these data demonstrate that particular methylation changes occur at specific loci in tumor associated tissues and that several of these markers are altered preferentially in high grade cancers.

Significance

By defining these epigenetic changes one can leverage this information to improve diagnosis and cure of high grade PCa. This analysis has the potential to provide an assay that will decrease the morbidity associated with PCa diagnosis and improve prognostication. This panel of markers can be used on non-cancer prostate biopsy tissue to validate negative findings and decrease in the near term the number and frequency of biopsies being performed in men with elevated PSAs. In addition, we envision the application of these markers to develop a non-invasive urine test that can be used as an adjunct to further identify men with a higher risk lethal PCa. The approaches to achieve these goals are described in detail below.

Confirm that Methylation Alterations Associated with a Field Defect in High Grade/High Volume PCa can be Detected in the Urine (Prophetic Example)

Prostate cells are shed into the urine. Previous small studies have focused on cancer-specific methylation alterations in the urine (Fujita K., Pavlovich C. P., Netto G. J., Konishi Y., Isaacs W. B., Ali S., De Marco A., Meeker A. K., Specific detection of prostate cancer cells in urine by multiplex immunofluorescence cytology, *Hum. Pathol.* 2009 July; 40(7):924-33; Rogers C. G., Gonzalgo M. L., Yan G., Bastian P. J., Chan D. Y., Nelson W. G., Pavlovich C. P., High concordance of gene methylation in post-digital rectal examination and post-biopsy urine samples for prostate cancer detection, *J. Urol.* 2006 November; 176(5):2280-4) and have demonstrated feasibility, but lower sensitivity because of the presence of rare cancer cells. In contrast, normal prostate epithelial cells are found within the urine at a much higher rate (Fujita K., Pavlovich C. P., Netto G. J., Konishi Y., Isaacs W. B., Ali S., De Marco A., Meeker A. K., Specific detection of prostate cancer cells in urine by multiplex immunofluorescence cytology, *Hum. Pathol.* 2009 July; 40(7):924-33). We seek to evaluate methylation changes found in normal cells associated with prostate cancer to determine if these changes predict the presence of cancer within this biofluid. Notably, our markers are also abnormal in cancer cells.

We will take validated tissue markers (six markers disclosed in Example 1 and others validated from the above described experiments in this Example) and apply them to urine specimens from men undergoing prostate biopsy throughout Wisconsin. We will confirm that methylation differences can be detected in the urine from men with cancer versus those without.

We envision that prospective urine samples from 250 men with high PSA values undergoing prostate biopsy will be obtained after an 'attentive' digital rectal examination. Of these samples 100 will be obtained through the Wisconsin Network for Health Research (WNHR). A further control group of 50 age-matched controls seen in the urology clinic with normal PSA values will be consented, obtained and tested. Briefly, after prostate examination, 20 ml of the initial stream will be collected, mixed with EDTA and stored on ice as described (Rogers C. G., Gonzalgo M. L., Yan G., Bastian P. J., Chan D. Y., Nelson W. G., Pavlovich C. P., High concordance of gene methylation in post-digital rectal examination and post-biopsy urine samples for prostate cancer detection, *J. Urol.* 2006 November; 176(5):2280-4).

Genomic DNA will be extracted from the pellet using a column as above. DNA will then be sodium bisulfite treated and quantitative Pyrosequencing performed using our panel of loci CAV1, EVX1, MCF2L, FGF1 and NCR2, as well as additional markers validated from the above described experiments in this Example. Methylation of individual loci will be compared between the TA and NTA groups using two-tailed student's t-tests conducted at a significance level of 0.026 (a rough false discovery rate). Additional analyses will be performed using logistic regression to determine if multiple loci, total PSA, free PSA, PSA density, or age improves the ability to predict which individuals belong to the TA group. Assuming that 150 of the 300 subjects belong to the TA group and the other 150 belong to the NTA group, we will have at least 80% power for detecting as significant a 0.3557 standard deviation shift in the mean methylation value between groups. Further subgroup analyses will be performed based on tumor volume, age, pathologic stage, and cancer grade.

In conjunction with the above approaches, we will seek to develop alternate technologies to quantitate methylation to permit widespread application. The original Nimblegen methylation arrays allows detection of methylation at specific sites, but not at basepair resolution. However, complete analysis of the prognostic potential of these sites will require a thorough analysis of the entire locus to identify specific nucleotides where methylation is predictive of disease course. Although the pyrosequencing approach is an established technique within our laboratory, one of its limitations is that it can only scan a limited number of methylation sites encompassing 100-300 bp within a single run and it is time consuming and expensive.

We will confirm alternate technologies which improve assay sensitivity and commercial applicability by: i) developing a methylation-sensitive qPCR multiplex approach based on amplification of multiple specific methylated loci (Campan M., Weisenberger D. J., Trinh B., Laird P. W. MethyLight. Methods Mol. Biol. 2009; 507:325-37), and ii) implementing direct sequencing of samples by utilizing next generation sequencing technology (available from the UW Biotech Center) to digitally detect methylation sites at basepair resolution. We will rely on methylation-specific priming combined with both methylation and unmethylation-specific fluorescent probes. This assay is faster with an accompanying ability to sensitively detect very low frequencies of hypermethylated alleles (Campan M., Weisenberger D. J., Trinh B, Laird P W. MethyLight. Methods *Mol. Biol.* 2009; 507:325-37). Direct sequencing utilizes established sequence capture techniques (for 25-30 loci) and then methylation analyses as described (Gu H., Smith Z. D., Bock C., Boyle P., Gnirke A., Meissner A., Preparation of reduced representation bisulfite sequencing libraries for genome-scale DNA methylation profiling, *Nat. Protoc.* 2011 April; 6(4):468-81). Briefly, the Agilent Sureselect™ system will be used to capture approximately 50 kb nucleotides surrounding each of these loci (approximately 0.1% of entire genome) for at least 100 of the samples. The enriched samples can be barcoded and sequenced in a high-throughput fashion using the Illumina HiSeq™ instrument (or a similar alternate machine) at the UW Biotechnology Center (80 million reads/lane) to identify specific sites of methylation by comparing sequences with bisulfite-converted material, thus providing a digital readout on the percentage of methylation at a specific site in a given sample.

We anticipate being able to detect methylation differences at one or multiple loci in men that have cancer and specifically high grade cancer. By increasing the pool of markers validated in tissues, we will decrease the likelihood that significant markers will not be detected in urine. Given the markers in TA prostate tissues identified so far are also abnormal in the cancer themselves, we anticipate the sensitivity of this approach will be much higher than approaches with markers specifically altered in cancer (Fujita K., Pavlovich C. P., Netto G. J., Konishi Y., Isaacs W. B., Ali S., De Marco A., Meeker A. K. Specific detection of prostate cancer cells in urine by multiplex immunofluorescence cytology. *Hum. Pathol.* 2009 July; 40(7):924-33). Statistical analyses for the methylated loci will likely be improved by the use of PSA, family history, digital rectal exam in statistical analyses.

We perform roughly 500 prostate biopsies a year at UW providing a larger pool of urine samples if necessary. Obtaining urine samples from the Wisconsin Network for Health Research (WNHR) will validate our finding to patients throughout Wisconsin. Roughly 10 ug of DNA can be extracted from 20 ml of urine using this approach (Rogers C. G., Gonzalgo M. L., Yan G., Bastian P. J., Chan D. Y., Nelson W. G., Pavlovich C. P., High concordance of gene methylation in post-digital rectal examination and post-biopsy urine samples for prostate cancer detection, *J. Urol.* 2006 November; 176(5):2280-4). The presence of competing cells of other etiology (including bladder, kidney and WBC) may have altered methylation changes. If this is encountered we will seek to enrich for the prostate cell population by utilizing antibodies to anti-NKX3.1 as described (Fujita K., Pavlovich C. P., Netto G. J., Konishi Y., Isaacs W. B., Ali S., De Marco A., Meeker A. K. Specific detection of prostate cancer cells in urine by multiplex immunofluorescence cytology, *Hum. Pathol.* 2009 July; 40(7):924-33). Given the cancer association of the markers identified, it would be unlikely other cell types will be altered in normal tissues from other sources.

Example 5

In an experiment analogous to Example 1, a subset of two genes was chosen for further evaluation, based on genomic location, putative biological function, extent of methylation and primer success in a separate validation using a set of 24 TA and NTA prostate specimens. Quantitative Pyrosequencing was employed to allow a more accurate evaluation of the extent of DNA methylation. Internal controls for the adequacy of bisulfite conversion were performed. Two loci, which were associated with the genes EXT1 and SPAG4 showed significant methylation changes ($P<0.05$). The locus associated with SPAG4 was hypermethylated and the locus associated with EXT1 was hypomethylated. The location of the probes and CG's assessed by Quantitative Pyrosequencing are shown in FIGS. **23** and **25**. The two loci in pyrosequencing are close or overlap the methylation array regions but sequences (FIG. 22) are different. The sequences listed in FIG. **20-21** have covered both array region (FIG. 22) and pyrosequencing regions. These data demonstrate that TA tissues have a methylation profile distinct from men without cancer (NTA) and that these changes alter specific regions of the genome.

Identification of a Widespread Methylation Field Defect in the Peripheral Prostate.

Preferential alteration in tissues adjacent to PCa tumor foci, i.e., field defect, suggests a peritumoral response. To evaluate whether tissues adjacent to PCa tumor foci are preferentially altered, the extent of field defect was assessed in 26 additional histologically normal tissues by looking at the methylation status of these two differentially methylated markers. The inventors micro-dissected normal tissues adjacent (TAA, 2 mm) and distant (TAD, >10 mm) from the main tumor focus for each of the specimens (FIG. **8**). Histological 3-dimensional H&E staining and AMACR expression determined by qPCR were applied to rule out any contamination by tumor cells or the presence of high grade prostatic intraepithelial neoplasia (HGPIN), a putative cancer precursor (Ayala, A. G. & Ro, J. Y. Prostatic Intraepithelial Neoplasia: Recent Advances. *Archives of Pathology & Laboratory Medicine* 131, 1257-1266 (2007)). Increased AMACR expression was found in two NTA and three TA tissues that were subsequently excluded from further analysis (FIG. **13**).

When compared to NTA tissues, hypermethylation of probes associated with SPAG4 and hypomethylation of EXT1 demonstrated significant changes in both TAA, as well as TAD tissues (FIG. **24** and Table 6). Notably, there was no difference in the extent of methylation seen at different distances from the tumor when TAA and TAD tissue sets were compared. Significant methylation changes were also seen in tumor samples when compared to NTA tissues for EXT1 and SPAG4, revealing a persistence of these changes in the associated cancer. These data indicate that the epigenetic field defect in the prostate is widespread and not solely localized to the immediate peritumor environment.

TABLE 6

Methylation Percentage Of All Analyzed CpGs For Each Gene

	EXT1			SPAG4		
	NTA	TAA	TAD	NTA	TAA	TAD
CG1	39.4	34.7*	34.2*	13.5	21.4*	25.2*
CG2	28.3	24.1*	24.5*	15.9	25.4*	27.3*
CG3	38.2	35.1*	35.0*	16.1	18.7*	18.1
CG4	27.2	24.3*	24.0*	11.6	15.9*	15.6*
CG5	14.8	12.8	14.0	9.0	11.5*	10.8
CG6	32.5	36.3	38.5			

*$P < 0.05$

Example 6

CpG Islands

Based on the teachings of Examples 1, 2 and 5, one can also check the CpG islands that are located in the promoter regions of the genes showing significant methylation changes correlating with PCa, preferably the region within about 5 kb upstream of the transcription start site (TSS), because the methylation of these CpG islands will change the gene expressions and affect gene functions. The inventors' primary research (data not shown) showed that one may wish to examine genes EXT1 and SPAG4. The expanded regions of each of these two genes for preferred screening of methylation changes are detailed in FIGS. **26-27**.

Both EXT1 and SPAG4 have CpG islands within the promoter regions. For EXT1, the expanded regions for preferred screening of methylation changes would be from 373 bps upstream to 84 downstream of transcription start site (TSS) FIG. **26** (SEQ ID NO:94). For SPAG4 the expanded regions for preferred screening of methylation changes would be from 1100 bps upstream of TSS through the first exon (SEQ ID NO:95), 1180 bps down stream of TSS (intron 1 and exon2, SEQ ID NO:96) and 3640 bps down stream of TSS (intron 9 and exon10, SEQ ID NO:97).

Example 7

DNA Methylation Urine-Based Screen for PCa

A widespread epigenetic field defect can be used to detect prostate cancer in patients with histologically negative biopsies (Truong et al., "Using the Epigenetic Field Defect to Detect Prostate Cancer in Biopsy Negative Patients" (2012) *J Urol*, in press). Prostate biopsies are performed on the patients who have elevated PSA levels. Prostatic massage will be given to each patient to increase the amount of prostate cells voided in the urine, and then voided urine will be collected from them. Those patients classified as having adenocarcinoma will be used in the positive biopsy samples, and the patients with this current biopsy negative and all previous negative biopsy will be used in the negative biopsy samples. The urine is centrifuged for 15 minutes at 1200 rpm at 4° C., the excess supernatant is removed and pellet at −80° C. immediately.

Genomic DNA from urine and biopsy tissue is extracted using Qiagen DNeasy Blood and Tissue Kit, Bench Protocol: Animal Tissues (Qiagen). The DNA is then treated with sodium bisulfite using the Qiagen EpiTect Bisulfite Handbook protocol (Qiagen, Valencia, Calif.) to modify the DNA to turn all the unmethylated cytosine to uracil. The bisulfite modified DNA is amplified by polymerase chain reaction

(PCR) using gene specific primers, with either the forward or reverse primer biotinylated. The genes amplified include CAV1, EVX1, WNT2, MCF2L, NCR2, FGF1, EXT1 and SPAG4. Five microliter of the PCR products will be applied for Pyrosequencing to ascertain the actual percent methylation within the gene. The assay is run in a PyroMark™MD Pyrosequencing System (Qiagen). All samples are analyzed with two independent trials and t-test will be used to test for differences in methylation between the positive and negative biopsy urine samples with $p<0.05$ considered statistically significant.

FIG. **28** shows methylation of the genes in urine from the patients who have either positive or negative biopsies for prostate cancer. We have tested the methylation for the six markers EVX1, CAV1, FGF1, MCF2L, WNT2 and NCR2. EVX1, CAV1, FGF1 and NCR2 showed significant methylation difference between the biopsy positive and negative groups, t-test *P<0.05.

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<212> TYPE: DNA
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 8

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<212> TYPE: DNA

<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 9

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<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 10

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<212> TYPE: DNA
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<212> TYPE: DNA
<213> ORGANISM: Homo sapiens

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<211> LENGTH: 2364
<212> TYPE: DNA
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 13

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<210> SEQ ID NO 14
<211> LENGTH: 1858
<212> TYPE: DNA
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 14

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<210> SEQ ID NO 15
<211> LENGTH: 43392
<212> TYPE: DNA
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 15

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<210> SEQ ID NO 17
<211> LENGTH: 3572
<212> TYPE: DNA
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 17

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agacaatgag tctgtttctt gtaatggctg accagattga agccctgggt tgtgctaaaa 3480

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ggaatgtttt gcaaatgtta aaaaaaaaaa aa 3572

<210> SEQ ID NO 18
<211> LENGTH: 1310
<212> TYPE: DNA
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 18

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acatgataag aaatatatat ttgggccagg cacattgtcc tgcacctgta atcacagaac 180

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<210> SEQ ID NO 19
<211> LENGTH: 2724
<212> TYPE: DNA
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 19

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gattacagaa aaaaaaaaaa aaaa 2724

<210> SEQ ID NO 20
<211> LENGTH: 3535
<212> TYPE: DNA
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 20

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<210> SEQ ID NO 21
<211> LENGTH: 6456
<212> TYPE: DNA
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 21

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<212> TYPE: DNA
<213> ORGANISM: Homo sapiens

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<211> LENGTH: 6236
<212> TYPE: DNA
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<400> SEQUENCE: 23

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gtccgcacag tgtccagcag caatttattc tttaaaggga gccggttccg atacagtggc   1140

cgagttgcaa aggaagtcat ggaatcaagt gctaagatca aacgggagcc accggaaata   1200

cacagagcag ggatggttcc cagccggagc tgtccctcca taacccatgg cccaaggctg   1260

agcagcgtcc ccaggacccg cagaagagct gttcacatct ccatcatgga aggcctagag   1320

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ggtggaccaa ggaacccggc tacccattcc cagcaatggg acccatcgcg gaaccatcgg   1980

cacatatacc aagtcctcct ctcatgactc aaagtccact gcagcctagg agggtgtttc   2040

ccagaagaag aaagggatag gctcatgccc tgtctaaaca aactgggaaa actcattttc   2100

ttcagaagtt atttcaagaa aggctcagcg actctgtttc tcatctttcc aatttgcagg   2160

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<210> SEQ ID NO 27
<211> LENGTH: 1618
<212> TYPE: DNA
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 27

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gctctgggat tgggttccgg attgctgaga ttttcatgcg ggcatctgag gaccagatgg    240

gacattgcag ctccagtggg acctgcctag caggggtagc tacctttatg gttattgtgg    300

gcaagcaacc cccgaaccag aagagccgag aaaccaaaga acaaggcaga cagatcccgt    360

ttgtctgtgt caggcacggc tgccatacgg tgattgccag taggagcctg ccgcgagtgc    420

tgacggccgc caggaagctg gctggggcca ccggccggcg ctgcctccct ctctctatgg    480

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aaaacactga ggtgctccca tctgtgcgtg gcccatgagc tgggatggtc ctccagctgc 1560
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<210> SEQ ID NO 28
<211> LENGTH: 4273
<212> TYPE: DNA
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 28

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aaaaaaaaaa aaa 4273

<210> SEQ ID NO 29
<211> LENGTH: 1922
<212> TYPE: DNA
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 29

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ttcaagcatc tggcaaaagc aagccccacc cagaacctct tcctctcccc atggagcatc 180

tcgtccacca tggccatggt ctacatgggc tccaggggca gcaccgaaga ccagatggcc 240

aaggtgcttc agtttaatga agtgggagcc aatgcagtta cccccatgac tccagagaac 300

tttaccagct gtgggttcat gcagcagatc cagaagggta gttatcctga tgcgattttg 360

caggcacaag ctgcagataa aatccattca tccttccgct ctctcagctc tgcaatcaat 420

gcatccacag ggaattattt actggaaagt gtcaataagc tgtttggtga gaagtctgcg 480

agcttccggg aagaatatat tcgactctgt cagaaatatt actcctcaga accccaggca 540

gtagacttcc tagaatgtgc agaagaagct agaaaaaaga ttaattcctg ggtcaagact 600

caaaccaaag gcaaaatccc aaacttgtta cctgaaggtt ctgtagatgg ggataccagg 660

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ctaaatgggc tttatccttt ccgtgtaaac tcggctcagc gcacacctgt acagatgatg 780

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ctcccatatg ctggagatgt tagcatgttc ttgttgcttc cagatgaaat tgccgatgtg 900

tccactggct tggagctgct ggaaagtgaa ataacctatg acaaactcaa caagtggacc 960

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aa 1922

<210> SEQ ID NO 30
<211> LENGTH: 1319
<212> TYPE: DNA
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 30

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gggaagagga caactcaaga aacgtattct tctctcccat gagcatctcc tctgccctgg 180

ccatggtctt catgggggca aagggaagca ctgcagccca gatgtcccag gcactttgtt 240

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ctggcactca gtacttgctt agaactgcca acagactctt tggagaaaag acgtgtgatt 360

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tccttgtgaa tgccatttat ttcaagggaa agtggaatga gcaatttgac agaaagtaca 600

caaggggaat gctctttaaa accaacgagg aaaaaaagac agtgcagatg atgtttaagg 660

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atgtggaaga ggagctgagc atggtcattc tgcttcccga tgacaacacg gacctcgccg 780

tgaaagagtg atggatcttg aagaatttga agctaactcc aggacaggca gaggacaaac 840

aaggatgctg atgaagtctt cttgcattcc ccatttctcg tctcatgctc ccttctcatg 900

cctcccttca tcttcagatg aaacacaatt ccctctcttt tactctgagt tgccctctga 960

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tcttttgtca aacaatctct cccactcaca gtagtatgta ttgcatgaag attaatgtaa 1080

tgaattggtt agaattttct aaactgttaa aaaatgtttt taacatttga aaggagttag 1140

gtacaaattg tttttattaa aaatttctgc ctgtctcaaa aaaaaaaaaa aaaaaaaaaa 1200

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aaaaaaaaaa aaaaaaaaaa aaaaaaaaaa aaaaaaaaaa aaaaaaaaaa aaaaaaaaa 1319

<210> SEQ ID NO 31
<211> LENGTH: 2831
<212> TYPE: DNA
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 31

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ccgctatcgc gatagcgccc gggcccgggg cgcgagaaaa aggcggcggg cgctcgcctc 180

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ccccgcctgt cgcgatacgc tcctcagcgg cggcgccagc tcctgtgcgt ccgtctccaa    240
gagagtatga agagagtgcg tctgtagggc agggaagatg gcggacaagc gcaaactcca    300
aggtgagatt gatcgctgcc tcaagaaggt gtccgagggc gtggagcagt ttgaagatat    360
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aaagaaggag attaagaagc tacaacggct gagggaccaa atcaagacat gggtagcgtc    480
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<211> LENGTH: 1329
<212> TYPE: DNA
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 32

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<212> TYPE: DNA
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 33

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<211> LENGTH: 3191
<212> TYPE: DNA
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 34

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<210> SEQ ID NO 35
<211> LENGTH: 2383
<212> TYPE: DNA
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 35

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<211> LENGTH: 7814
<212> TYPE: DNA
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 36
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attccccctc agactcccac ggtcctcccc aggcttaacc ccctcaagcc tctttccact 840

gtccccctat gccggggaaa cccattctct tccttttcct tctgagaccc ctccctctct 900

ttctccagca ttctggctgg ggcttctgta cctggtctct cctttggaga atgtgagttg 960

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ctggactgtc ggtctgctgg ggtgggggta 1050

<210> SEQ ID NO 40
<211> LENGTH: 1455
<212> TYPE: DNA
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 40

cgattgatgg cgacgtccgt ggggcaccga tgtctgggat tactgcacgg ggtcgcgccg 60

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cggaagctgc cttttagagc ctttcgcaca gatgccagaa aaatccacac tgcccctgcc 180

cgaaccatgt tcctgctgcg tcccctgccc attctgttgg tgacaggcgg cgggtatgca 240

gggtaccggc agtatgagaa gtacagggag cgagagctgg agaagctggg attggagatt 300

ccacccaaac ttgctggtca ctgggaggtg gctttgtaca agtcagtgcc aacgcgcttg 360

ctgtcacggg cctggggtcg cctcaatcag gtggagctgc cacactggct gcgcaggccc 420

gtctacagcc tgtacatctg gacgtttggg gtgaacatga aagaggccgc tgtggaggac 480

ctgcatcact accgcaacct cagcgagttc ttccggcgca agctgaagcc gcaggcccgg 540

cctgtctgtg gcctgcacag cgtgattagc ccatcggatg gaaggatcct caactttggg 600

caggtgaaga actgtgaggt ggagcaggta aagggggtca cctactccct ggagtcgttc 660

ctgggcccgc gtatgtgcac agaggacctg cccttcccac cagccgcgtc gtgtgactcc 720

ttcaagaacc agctggtcac ccgggaaggg aatgagctct atcactgtgt catctacctg 780

gcccctgggg actaccactg cttccactcc cccaccgact ggactgtgtc ccaccggcgc 840

cacttcccag gctccctgat gtcagtgaac cctggcatgg ctcgctggat caaagagctc 900

ttctgccata acgagcgggt ggtcctgacg ggggactgga aacatggctt cttctcactg 960

acagctgtgg gggccaccaa cgtgggctcc attcgcatct actttgaccg ggacctgcac 1020

acaaacagcc caaggcacag caagggctcc tacaatgact tcagcttcgt gacgcacacc 1080

aatagagagg gcgtccccat gcgtaagggc gagcacctgg gcgagttcaa cctgggctcc 1140

accatcgtgc tcatcttcga ggcccccaag gacttcaatt tccagctgaa aacaggacag 1200

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taagggatct tttccaaaca gagtgagggt cttttcaaga gggaggccca tgaggccatc 1320

caggtaaggg cctgcctcag cgtggttggg agtctgacca ggtaggactt gaatgattcg 1380

gctaccacct gttccagagg tgcagacaag aggtggcgag agcccccatc atgcccctca 1440

accctatccc gttcc 1455

<210> SEQ ID NO 41
<211> LENGTH: 4683
<212> TYPE: DNA
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 41

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acaccccaac gatgaataca gccctctgct tttgcaggtc aagtctctta aggaagattt    240
acagaaggaa actatcagtg tggaccagac tgtgactcaa gtgttccggc tgagacctta    300
tcaggatgtc tatgttaatg tcgtagaccc taaggatgtg acccttgacc tagtggaatt    360
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gtg 4683

<210> SEQ ID NO 42

<211> LENGTH: 3047
<212> TYPE: DNA
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 42

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gtctgggtag gagccagtca tctccatcca tccacagcca tgaatttcct ccggcgacgt    180
ctctctgaca gcagcttcat ggccaacctg cctaatggct atatgacgga cctgcaacgc    240
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aagcaggccc ctcaggccac ctcaggactg atggagcctc caggtccctc cacgcccatt    420
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gagttgaacc tagctgccta tgtgaccggg ggctgcatgg tggacatgca ggtcgtgaga    600
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caaacatttt tccccaacca taagccaatg gtcacagccc cacacttccc ggtggtagtc    900
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tcacagcccc ggcccccctgt gcagggccgt agtacctccc agcagggtga agagtccaag   1740
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tcctgatggg aacagaatgg agggcctgag aacatacttt ctaaatgcct ttgacccagg   2040
aaccgattat ctatatttgt tcccattttc cttcaccgtg acattccagc attgtctgac   2100
tgtgaggtgg gcctttgaga gcctccaggt tcctcaaaac aggcctgagc gatgggcatc   2160
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```

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agtggctagt tttcacattc ttactagtgt ttggctcacc tttgggcaaa ggccccctct   2280

aggccttgcc ccacctccat caaacgcaga cactgtagtc agacctcagc aatataggag   2340

gcaataatct tttaacagtg ttttgcaaac aaacaaaaag agaaaaatcc cagccagggg   2400

aactcgccac ctgcccacgc tagttccatc cacgctcaag acccgccctt agaccaggca   2460

ggcaaaggcc cccatcacac tcggccacta gtggggtcct gaggccaaga aagaaaccag   2520

accctgtatg acaagtgggg tctttcagaa cacgacagaa acagggggc ccttgtaatg    2580

ccactcatac tcagagcatt attcttattt ggacagccaa gggcagatca caggttattg   2640

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aggaatgccg tttccttttt atggatctgt tgggaaccag agagaatcaa cagatcaatg   2820

acataggatc cgaagtgcaa tgatagtcac ttctagtttg gcatttcaca aactctgtac   2880

agcaaggtat tggtaggtta ctcaatttca aaagggcccc atggccaaat atgtttagga   2940

accgctgttt gtatttcttt ttttggagac gcattgtata taatatatgt caaaggcttt   3000

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<210> SEQ ID NO 43
<211> LENGTH: 30
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: synthetic oligonucleotide

<400> SEQUENCE: 43

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gggtaatatt tataagttta ataataaggt                                      30
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<210> SEQ ID NO 44
<211> LENGTH: 21
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: synthetic oligonucleotide

<400> SEQUENCE: 44

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taaaaactat cccaaccctt c                                               21
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<210> SEQ ID NO 45
<211> LENGTH: 25
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: synthetic oligonucleotide

<400> SEQUENCE: 45

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aagtttaata ataaggttat ggtag                                           25
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<210> SEQ ID NO 46
<211> LENGTH: 31
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: synthetic oligonucleotide

<400> SEQUENCE: 46

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ggaggagagg aagttaggag tttataaagg a                                    31
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<210> SEQ ID NO 47

<211> LENGTH: 27
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: synthetic oligonucleotide

<400> SEQUENCE: 47

caaatacaac ccaaaaccaa aaacaat 27

<210> SEQ ID NO 48
<211> LENGTH: 23
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: synthetic oligonucleotide

<400> SEQUENCE: 48

gaagttacga gtttataaag gat 23

<210> SEQ ID NO 49
<211> LENGTH: 24
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: synthetic oligonucleotide

<400> SEQUENCE: 49

ggatgggata gtgaagataa gagt 24

<210> SEQ ID NO 50
<211> LENGTH: 30
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: synthetic oligonucleotide

<400> SEQUENCE: 50

ttcaacatac tatcatctaa tcctttacac 30

<210> SEQ ID NO 51
<211> LENGTH: 22
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: synthetic oligonucleotide

<400> SEQUENCE: 51

tttttttaag gttatgtgat aa 22

<210> SEQ ID NO 52
<211> LENGTH: 30
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: synthetic oligonucleotide

<400> SEQUENCE: 52

gagttgagtt ttattttggg tattttgaag 30

<210> SEQ ID NO 53
<211> LENGTH: 29
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: synthetic oligonucleotide

<400> SEQUENCE: 53

acccccaaat tactaaacta atatattcc 29

<210> SEQ ID NO 54
<211> LENGTH: 25
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: synthetic oligonucleotide

<400> SEQUENCE: 54

caaattacta aactaatata ttcca 25

<210> SEQ ID NO 55
<211> LENGTH: 28
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: synthetic oligonucleotide

<400> SEQUENCE: 55

gttgtgggag agtaaggttt ggaaataa 28

<210> SEQ ID NO 56
<211> LENGTH: 23
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: synthetic oligonucleotide

<400> SEQUENCE: 56

ctcatctcca ccccttcat ttt 23

<210> SEQ ID NO 57
<211> LENGTH: 15
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: synthetic oligonucleotide

<400> SEQUENCE: 57

cccccttcat tttct 15

<210> SEQ ID NO 58
<211> LENGTH: 26
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: synthetic oligonucleotide

<400> SEQUENCE: 58

ttttggaggt atagggtagg aaataa 26

<210> SEQ ID NO 59
<211> LENGTH: 24
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: synthetic oligonucleotide

<400> SEQUENCE: 59

aattcaaaat catccaaacc caaa 24

<210> SEQ ID NO 60
<211> LENGTH: 23
<212> TYPE: DNA

<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: synthetic oligonucleotide

<400> SEQUENCE: 60

aggaaataat ttttaattga ata 23

<210> SEQ ID NO 61
<211> LENGTH: 200
<212> TYPE: DNA
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 61

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gggcatctct gcaggcgcgt cggctccctc cacccctgct gagatgatgc actgcgaaaa 180

cattcgctct ccccgggacg 200

<210> SEQ ID NO 62
<211> LENGTH: 802
<212> TYPE: DNA
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 62

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cgcgaggacc cagcagtctg gcgcccccac cacggcctgg aagatgacgg agggcccaag 120

actaatattc acgacagcca gaccacgctt attgtttaga aggaagctcc ctttgttctt 180

actttttaac caaagagaag cgaaaacatt tttttcctga tcacattttc accgacacct 240

gagccgacaa gccagctcct ggcccccggc tcaggactcc tcgctctctc ccttctcggg 300

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gccccagcgg gggaagggac ggggggcctg ccgtgtggca ggtgggggat gggtgtcccc 720

cgccgcgaga aatgagaagc cgccgggcct ggagcggcct ccacctcagc tgctatcacc 780

ccctctccgc tgtcatggga tt 802

<210> SEQ ID NO 63
<211> LENGTH: 200
<212> TYPE: DNA
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 63

tttttgtct tctttccttt aaaaacccaa ccgctcttaa tgtgaggttg atgaaaggat 60

gcttttggaa gaagtgacat ttggttaaaa cgttttcccc ctaatgcgcc ggtggaaagg 120

ggcgggggtg ggtgtggttc cctaggctcc taagactggc cagtcagctt tgaaagagcg 180

gggcagaagt cgggagaggg 200

<210> SEQ ID NO 64
<211> LENGTH: 200

<212> TYPE: DNA
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 64

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cccaaaatag cgcggtgaaa gctactgcct tctcccaagt aggggcctcc agtactgcca 120

cagcaggggc cgcattcctg gcgcctcttc attcgaaaaa cctctttcca ggagacttcg 180

ctgattctga acgaatactt 200

<210> SEQ ID NO 65
<211> LENGTH: 400
<212> TYPE: DNA
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 65

actataaggg ggagtactgc gtcaccttca tctttttatc cctttggcct tgctccgtgc 60

ctgaaagctc accacactgg aacgtccagg tgcacatgtg ccactggaca ccgggatgtt 120

gccggatgct cttttggacg ctggaatgct ggtgcattgt tgccggatgc tggaatggtg 180

cacgcacgct ctgttggacg ctggaatgct ggtgcattgt tgccggatgc tggaatggtg 240

cacgcatgcc ctgttggact ctggaatgct ggtgcattgt tgccaaatgc cggaatggta 300

cacggatgct ctgttggacg ctggaatgct ggtgcattgt tgccggatgc tggaatggtg 360

cacgcatgct ctgttggacg ctggaatgct ggcgcatgtg 400

<210> SEQ ID NO 66
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<212> TYPE: DNA
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 66

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gccctgtgat ggcggccatg gccctgcata gacacgagct ggaatctgca ggtggcagcc 120

aggacgctgc gtgtgtcgag tgcacagtgt ggcttggtgc caaccatggc gagggtggag 180

agccccgtgc ctgcagcgcg cgcttccctc actgggtcct gcgtccttgg gcaggcgatg 240

cccctgcggg gaggggctgg tccatccccg gccagccacg gacccacgca tggacccagc 300

gacccacgga cctgcttacc tgggcgcggc gcgggtggca tgcggccaca cggaaggggc 360

gcgctgggct gctgcggcct ctgcagcttc tacacctgcc acggggcggc cggaggtaaa 420

gggaggcggc ggccaggcgc ggccccgcgg aggcagctgc actcgctcgg tccactcgcg 480

gcttcgcggc tgcccgcaaa ccaggagggc gtggagaccc ggaaccgggg ggaagggcgg 540

gggcacttgt gcggcacccg cggggctccc aggggacctc ggcggtgaca cgaatttcta 600

ggtgaccttg gcggtgacac gaatttctag gtgacctgtg tgatacacta ggtgacctag 660

tgacacaggt gacacttcca ggtgaccgcg gcggtgaccc gcggggctcc caggtgacct 720

cgttggtgag ccccggggct ccccgacgac cgcggcggtg acacgcgggg ctcccaggtg 780

accccggcgg tgcactcaca ggactcccag gtgacccgcg gtggtgacac accggggcgg 840

gcgcgcgccg cttccgcttc cgccgagccg ccccccgccc cccgcggcgc agcgcgcgcc 900

cccctcccgg tggcgcggaa ccaatcctgg gcagggaggc ggcggctgga ggctgaaagc 960

gctgccgtgg ccccctcccc gcctccgccg cgccccctcc 1000

<210> SEQ ID NO 67

<211> LENGTH: 210
<212> TYPE: DNA
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 67

gcttctcctg tgcctgcctc atattctggg ttctctccag agctcgcgtc cactgcctgc 60

cagtcagcag atggatgact ctgttcacct cagccgcgac acgccccaca gcgagtgcag 120

cagtcgtcct gccagatggg ctgctcctgg ctgcgtccat tctctcagta aatagcctct 180

ccattcatcc ttccggtccc tctatgcccg 210

<210> SEQ ID NO 68
<211> LENGTH: 566
<212> TYPE: DNA
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 68

agccgctcct gtcatcttcc ctttctctct ccccatcagc ctgcgaggga ctaaaagccg 60

gcgatttttc cttgctgtat ttctttcttt tttttttttt ttttttgaga cggagtctcg 120

ctctgtcccc caggctggag tgcagtggcc cgatctcagc tcactgcaag ctccgcctcc 180

caggttcaca cctttctcct gcctcagcct cccaagtagc tgggactaca ggcgcccgcc 240

accgcgccca gctaattttt tgtattttta gtagagacgg ggtttcaccg agttagccag 300

gatggtctcg atctcctgac ctcatgaccc gcccacctcg gcctcccaaa gtgctgggat 360

tacaggcgtg agccaccgcg cccggcctgt ttctttctct tttttcttga gaccgagtct 420

cgctctgttg cccaggctgg agtacagtgg catgatctca gctcactgca acctctgtct 480

cccaggttca agcaattctc ctgcctcagc cttccgagta gctgggacta aaggctcccg 540

tcaccaccgt tgcccagcta attttt 566

<210> SEQ ID NO 69
<211> LENGTH: 200
<212> TYPE: DNA
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 69

gattattttg gaatagcaca gggttttgtt ttttttttcgt tttttggttt ttcttgagac 60

ggagtttcgc tgttgttgct caggctggag tgcaatgcca caatctcagc tcatcacaac 120

ctccgcctcc cgggttcaag cgattctcct gcctcagcct cctgagtagc tgggattaca 180

ggcatgcgcc accatgcccg 200

<210> SEQ ID NO 70
<211> LENGTH: 340
<212> TYPE: DNA
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 70

cctccttcat gggtattcca cattgcttac acagtgacag ggattaaaaa caaaactaaa 60

ggctgggcgt ggtggctcac gcctgtaatc ccagcacttt gggaggctga ggcgggtgga 120

tcacgaggtc aggagatcga gaccatcttg gctaacacgg tgaaaccccg tctctactaa 180

aaatacaaaa aattagccgg gcgcggtggc aggcgcctgt agtcccagct actcaggagg 240

ctgaggcagg agaatggcgt gaacctggga ggcggagctt gcagtgagcc gagattgtgc 300

cactgcaatc cggcctgggc taaagagcgg gactccgtct 340

<210> SEQ ID NO 71
<211> LENGTH: 200
<212> TYPE: DNA
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 71

atgtattgat gatcacattc actactcaca cttacaaagt acagctccca ggccgggcgc 60

ggtggcttac gcctgtaatc ccagcacttt gggaggccga ggcaggcgga tcacgaggtc 120

atgagttcaa gaccagcctg gccaacatgg tgaaacccca tctctactaa aaatataaaa 180

attagcctgg tgtggtggcg 200

<210> SEQ ID NO 72
<211> LENGTH: 200
<212> TYPE: DNA
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 72

gttgtgaact tgtgtttttc cgttttatat gtatatgcca cttgtttttt tgttttgttt 60

tatttcgttt tgaggcggag tctcgctctg tctggagtgc agtggtgcaa tctcggctca 120

ctgcaacctc cacctccagg gttcaagcga ttctcctgcc tcagcctccg gtgtagctgg 180

gactacaggc gcctgccacc 200

<210> SEQ ID NO 73
<211> LENGTH: 200
<212> TYPE: DNA
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 73

aagtagctgg gattacaggc gcctgctacc acgcctggct aatttttttgt attttagtag 60

agacgtggtc tcaccatgtt ggccaggctg gtctcaaact cctgacctca agtgatccac 120

ctgcctcggc ctccaaaact gccgggatta caggcgtgag ccaccacgcc tggccgctaa 180

caagtaattt taaagtatca 200

<210> SEQ ID NO 74
<211> LENGTH: 200
<212> TYPE: DNA
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 74

tttaactttt gaacttttcc gaagctttcc atattttcta tgtcctccaa gtgcccatca 60

tatcttttat tttctccttt cattgacctc tgtctttctt cagagctttc tggaaacctt 120

tgccgcttct cggccaccca cttgcttaga agccccatgc gggccgcggg gtgctgtggg 180

ctccaggcgg attgggcggg 200

<210> SEQ ID NO 75
<211> LENGTH: 200
<212> TYPE: DNA
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 75

ccagaatccc aactcagtaa gaccttgtaa atccatgaca ttagccccaa ttcccactcg 60

tcccaaatcc cataaccttt ccaccctgca cctgaagtgc gcagtcatca gcacaagctc 120

ctgtatgctc agcttctctg aacgtcaccg cggtactctc cctgacatct gcctgttctc 180

cgaggacaat gctttctccg 200

<210> SEQ ID NO 76
<211> LENGTH: 1002
<212> TYPE: DNA
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 76

gccaaccacc ttttctttcc taagtgtctg gatttacttc aagaaaatgc gggacaaaga 60
agggtggagg taagctttcg tttattcccc tgcttcacgg gggaaggagg tttgtgagca 120
taagcatgta agtacatgag aggcgtgttg ctctttggtg cctatcatac cctccccatg 180
gccggcgtgc acacacggcg agcagaaacg ctcccccgcc ccgctgcctg ccgccccacg 240
cgccctccct gcacctcccg cccgaccgac gcagaccaag cagaacttcc ctgggtcgcg 300
gcccagcgat acggagcggc cctggcgagg agccctgctc ttcccgagtc gtgggtggcg 360
cggtgcttgt ttccctcccc tccctttccg gacccaaacg gggatgtatc tgggtcagcc 420
tgggaggggc cggacctgcc agggaccagc gtgggggaag gggtggcga tgacagcatc 480
tttcaggttt ttggcgtctc tgagcttcgc ctcgtccagc ctctcaccgc gctcgctgcc 540
ggcgagggct gacgctctgg ccagtccagg cccgagggtg ggctggagag agggagagcc 600
cgtccttccg atctgggcgg cacccctcc cccacgccct gcgaacaatt cgcctcccac 660
acatacacac aggcgcatac tctattcccc agagcacgct cctcgggcgg gcagtgagtc 720
cctccgcccc aggaaaagag caatggaaca gttcacggcc gccacgagtt cctggtcttc 780
cttcctttcc ggtgataaac ggcgcggcta caagccagct actgctcaaa atgctccacc 840
cgcgggccca agcccctctc tcttggctgg gcgggggccc aggtccagga ccgagggtcc 900
cttaacctcc acaaggcgca caggctgagc gcccaggcgg caggaggtgc aagggcgcac 960
acccccggcg aacgcctggc tgcctcggtt cctctctatg tg 1002

<210> SEQ ID NO 77
<211> LENGTH: 400
<212> TYPE: DNA
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 77

atagacgcgg cagctccaaa tttacaagtg ctagctcttc atcccagctt cagggagaga 60
agcgaagcaa tgagttgaga atcatctctg gattcttgta tcccatgcat agtaatctcc 120
ttatcccctg gccccccttcc tcgtttcctc acattgcacg ctcagggact tgtttgccag 180
cggatggcct cggcaatccg gaacgcacgc tccgagagcc cacggatgct ctttggcctg 240
gagcttccct aaaggttcct gtattcgcgt gtgctcgtaa ccatgcagcg atgttccccc 300
ttccccgcct cacctcatcc ccagacatct cttgccatca tttcatgcac ccgtgtctaa 360
aaccccgcgt ttctccccac ccccgccagg cgcagcaccc 400

<210> SEQ ID NO 78
<211> LENGTH: 50
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: synthetic oligonucleotide

<400> SEQUENCE: 78

atcgacctgg tcaaccgcga ccctaaacac ctcaacgatg acgtggtcaa 50

<210> SEQ ID NO 79
<211> LENGTH: 50

<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: synthetic oligonucleotide

<400> SEQUENCE: 79

ttgtcacttc ccgggcttcg cggcgccagg tcggaaatgg tcccaatggt 50

<210> SEQ ID NO 80
<211> LENGTH: 50
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: synthetic oligonucleotide

<400> SEQUENCE: 80

tcttctcctg gggaggaggc gtggctcgga gcagacgtga cttctgtttt 50

<210> SEQ ID NO 81
<211> LENGTH: 50
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: synthetic oligonucleotide

<400> SEQUENCE: 81

acaagctatg ataagtgctg tgaaggttgt gccaagggct gggggggatgg 50

<210> SEQ ID NO 82
<211> LENGTH: 62
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: synthetic oligonucleotide

<400> SEQUENCE: 82

gtttcctcac ctgtagagag agaaatatta tatcacactg ttgcaaggac taagataagc 60

ga 62

<210> SEQ ID NO 83
<211> LENGTH: 52
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: synthetic oligonucleotide

<400> SEQUENCE: 83

gtttcctaag tttccttcaa actctgtctg catccgcaca tttgatctct ag 52

<210> SEQ ID NO 84
<211> LENGTH: 50
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: synthetic oligonucleotide

<400> SEQUENCE: 84

ttataatcag ggaagggcac tgtacacaag cccagtgagt agaaaggctg 50

<210> SEQ ID NO 85
<211> LENGTH: 57
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: synthetic oligonucleotide

<400> SEQUENCE: 85

cggcagaagc tggcattaca tttctaagaa cggggaaatc gttattcaat tagagat 57

<210> SEQ ID NO 86
<211> LENGTH: 50
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: synthetic oligonucleotide

<400> SEQUENCE: 86

caccatcctc ccggcatgtg gatatggtta tcaacctgga ggctctccaa 50

<210> SEQ ID NO 87
<211> LENGTH: 50
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: synthetic oligonucleotide

<400> SEQUENCE: 87

atctgattga gtcatgttgg caagagctgg gtctaggacc ctggggtggg 50

<210> SEQ ID NO 88
<211> LENGTH: 30
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: synthetic oligonucleotide

<400> SEQUENCE: 88

taggagttag agattagttt ggttaatatg 30

<210> SEQ ID NO 89
<211> LENGTH: 30
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: synthetic oligonucleotide

<400> SEQUENCE: 89

ccaaattttt aaaacaaaat ctcactctat 30

<210> SEQ ID NO 90
<211> LENGTH: 19
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: synthetic oligonucleotide

<400> SEQUENCE: 90

caactcacta caacctcca 19

<210> SEQ ID NO 91
<211> LENGTH: 26
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: synthetic oligonucleotide

<400> SEQUENCE: 91

ggtaggagaa gtgttggtta gtatgt 26

<210> SEQ ID NO 92
<211> LENGTH: 20

<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: synthetic oligonucleotide

<400> SEQUENCE: 92

cctaaaccca actcttacca 20

<210> SEQ ID NO 93
<211> LENGTH: 24
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: synthetic oligonucleotide

<400> SEQUENCE: 93

ttagtatgta taggttagag gaag 24

<210> SEQ ID NO 94
<211> LENGTH: 458
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: synthetic oligonucleotide

<400> SEQUENCE: 94

cgtcctcccc gcgggcagtg ccggccccga gcagcgcttc gcaggccccc gcgcgaacgc 60

tgccgaccgc cgcgttcggt cgccgaatgt tacccggttc tgaatgttac acttacacat 120

tccattcccg acacgacagc gctgacctca tccatccacg cagcccgcgc tgccattggc 180

cgagcgtcac gtccgggggg ggcggtgctt ccgctgcgcc cattcataac ccccggccgc 240

gggccgaggc gccggcgcgg cgttgggggc gtagggggcg cagggagccg gggctcccgg 300

gttgcaagct gccggcgggc tgccgggcag gtggagcgcg ggacggcccg gtgcgagccc 360

cgcggcccct cggcgcgccc aggcccggat ctcggcctgc gccgtgccgg ggaccagagg 420

cgcctgcgga aacgcggcgg ccggggaagg aggcaccg 458

<210> SEQ ID NO 95
<211> LENGTH: 2190
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: synthetic oligonucleotide

<400> SEQUENCE: 95

gaggtcagga gttcacgacc agcctggcca acatggtaaa accccgtctc tacaaaaata 60

caaaaattag ccaggcatga tggcgggtgt ctgtaatccc aactactcgg gaggctgagg 120

caggagaatc gcttgaaccc gggaggcgga ggttgcactg agccgagatt gcactactgc 180

cctccagcct gggcgacaca gcaggactct gtctcaaaaa ataaaaataa aataaaaata 240

aaaatgctgg gcgcagtggc tcatgcctgt aatcccagca ctttaggagg ccggggcggg 300

tggatcacct gagatcggga gttcaagacc agcctgacta acatggagaa accccgtctc 360

tactaaaaat acaaaattag ccaggcatgg tggtgcatgt ctgtaatccc agccactcag 420

gaggctgagg cgggagaatc gcttgaaccc gggaggcgga ggttgcagtg gaccaagatc 480

gcgccattgc actccagcct gggcaacaga atgagactcc atctcaaaaa aaaaaaaaaa 540

agaaagaaag aaagaaagaa agaaagaaag aaagaaagaa agaaagaaag aaagaaagaa 600

agaaaaaaac tgttatagac tgagtgccat tttagatggg gttttctggg aagtgctgtg 660

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acatcatcgc ttgctgtaaa agaggccggg cgcggtggct gacgcctgta ctcccagcgc    720

tttgggaggc cgaggcggga ggatcgcttg agcctaggag ttcgaagtta caatgagcta    780

tgatcaggcc actgcactcc agcctgggca atgagaaaga ccctgtctct taaacaacaa    840

caaagtcaga aggagaggct gccatggcta cggctccagg tgacgtcacg gccagctccg    900

tgacgcgcgg ccagggcagc ccgcggagac cgaggctcct ctgtgacgtc agcagccggc    960

cgggacacag cgggagggca ggtgcggccg cggggcctgc cgacttcacg cagggtccgt   1020

ggggtccccg cggcgcgcag cggctgaagg aggccccagg gccttggcga ccgcagcggc   1080

ggctttagcg tcagtgacta ggcagcaggg ggtcaggatg cggcgaagct cccgcccggg   1140

ctcggcctcg tcctcgcgca agcacacgcc caactttttc agcgagaaca gctcaatgag   1200

catcacctcg gaggacagca aagggctccg gtcagcggag cccgggcctg gggagcccga   1260

gggcagaaga gcccggggcc cgagctgcgg tgagcccgcc ttgagcgcgg gagtgcccgg   1320

aggaaccaca tgggcaggaa gctctcagca gaagccagcg cctcggagcc acaactggca   1380

gacagcctgt ggcgcggcaa ccgtgagggg cggggcctcg ggtgcgggcg gggtcgaccc   1440

cgggtgagcc agtggagggg gcggggccta aagggcggtg ctgggcgggg acggggctaa   1500

gatgatatct gggcacctcc tacaaggtgg gtcctgtagg gtaaagggat ggtgctaaat   1560

gagatccctt aaggggcgga gcctcggtgt cctggacggt tatgggaagg ggcggggaaa   1620

atcttgtggt tgggtgccac tgagggggcg cggcctcaat gttagcgtga gtggctccca   1680

ggacaattgg gttccaccaa gatctaaggc tgggggcggg tcatccgttt gggggaggga   1740

ccaactcttt tttttttttt tttgcaacgg agtttcgctc ctgttgccca tgccatgcaa   1800

tggcatgatc tcggctcacc gcaacctccg cctcccgggt tcaaacgatt ctcccgcctc   1860

agcctcccga gtagctggga ttacaggcgt gcgccaccat gcccggccaa tttttgtgtt   1920

tttagtagag acggggtttc tccgtgttaa tcaggctggc ctcgaactcc cgacctcagg   1980

tgatccgccc gcctcggcct cccaaatcgc tgggattaca ggcgtgagcc accgcgcccg   2040

gccaggagac caactcttga cggagcctcc ctgaggggcg gggcttcaga gggcggagct   2100

ggagccggga tagggctgcg gtgggaccaa agcctgtgag agacttccca gctgtctggc   2160

ttgtggactg agcaatctgc ggcccggtct                                    2190
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<210> SEQ ID NO 96
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<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: synthetic oligonucleotide

<400> SEQUENCE: 96

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gttcccgcag aaccgactgg gtctccagta gtctctgagg agccgctcga ccttctcccg    120

accctggatc tgaggcagga gatgcctccc ccgcgggtgt tcaagagctt tctgagtacg    180

ggccaggcca gctgcgatcc cctctgaccc tcgggttccc ctctccgaac tccagttctc    240

tctgagcccc cggcccccgt ttgagtatcg agcccctctc cg                       282
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<210> SEQ ID NO 97
<211> LENGTH: 234
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: synthetic oligonucleotide

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<400> SEQUENCE: 97

cggcagcagt cgctctgtcc gacggttccg atggtccctc cgcccgcctg cagccccacg     60

tgttccctgg gaattgctgg gcttttgaag gcgaccaagg ccaggtggtg atccaactgc    120

cgggccgagt gcagctgagc gacatcactc tgcagcatcc accgcccagc gtggagcaca    180

ccggaggagc caacagcgcc ccccgcgatt tcgcggtctt tgtgagtgcg gacg          234
```

We claim:

1. A method of amplifying at least one of the eight target DNA sequences comprising the steps of:

(a) providing a reaction mixture comprising: (i) a double-stranded bisulfite modified target DNA; wherein the target DNA is from histologically normal prostate tissue of the a subject and (ii) at least one pair of primers selected from the group designed to amplify at least one gene selected from the group consisting of SEQ ID NO:1, EVX1, MCF2L, FGF1, WNT2, NCR2, EXT1 and SPAG4, wherein the primer pair comprises a first and a second primer that are complementary to the target DNA sequence, (iii) a polymerase and (iv) a plurality of free nucleotides comprising adenine, thymine, cytosine and guanine;

(b) heating the reaction mixture to a first predetermined temperature for a first predetermined time to separate the strands of the target DNA from each other;

(c) cooling the reaction mixture to a second predetermined temperature for a second predetermined time under conditions to allow the first and second primers to hybridize with their complementary sequences on the target DNA and to allow the polymerase to extend the primers; and,

(d) repeating steps (b) and (c) at least 10 times wherein an amplified target DNA sample is formed.

2. The method of claim **1** wherein (v) PCR reaction buffer and (vi) $MgCl_2$ are additionally added to step (e).

3. The method of claim **1** wherein the primers are methylated.

4. The method of claim **1** wherein the primers are not methylated.

5. The method of claim **1** wherein the primer pairs are designed to amplify one target.

6. The method of claim **1** wherein the primer pairs are designed to amplify 2, 3, 4, 5, 6, 7, or 8 gene targets.

7. A method of amplifying at least one of the seven target DNA sequences comprising the steps of:

(a) providing a reaction mixture comprising: (i) a double-stranded bisulfite modified target DNA; wherein the target DNA is from histologically normal prostate tissue of the a subject and (ii) at least one pair of primers selected from the group designed to amplify at least one gene selected from the group consisting of EVX1, MCF2L, FGF1, WNT2, NCR2, EXT1 and SPAG4, wherein the primer pair comprises a first and a second primer that are complementary to the target DNA sequence, (iii) a polymerase and (iv) a plurality of free nucleotides comprising adenine, thymine, cytosine and guanine;

(b) heating the reaction mixture to a first predetermined temperature for a first predetermined time to separate the strands of the target DNA from each other;

(c) cooling the reaction mixture to a second predetermined temperature for a second predetermined time under conditions to allow the first and second primers to hybridize with their complementary sequences on the target DNA and to allow the polymerase to extend the primers; and,

(d) repeating steps (b) and (c) at least 10 times wherein an amplified target DNA sample is formed.

8. The method of claim **7** wherein (v) PCR reaction buffer and (vi) $MgCl_2$ are additionally added to step (e).

9. The method of claim **7** wherein the primers are methylated.

10. The method of claim **7** wherein the primers are not methylated.

11. The method of claim **7** wherein the primer pairs are designed to amplify one target.

12. The method of claim **7** wherein the primer pairs are designed to amplify 2, 3, 4, 5, 6, or 7 gene targets.

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