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(54) Title: MATERIALS AND METHODS FOR IDENTIFYING PATIENTS SUSCEPTIBLE TO DEVELOPING TAXANE INDUCED NEUROPTHY

(57) Abstract: A randomized phase III study with a planned accmal (n=4950); GWAS performed ors 2204 patients to compare genotypes with efficacy and toxicities. The phenotype for this study is time to first grade 2-4 neuropathy. GVVAS is conducted using the Xnfmium HumanOmnil platform from Illumma which assessed 1.2 million SNPs per patient. Comparisons are made using Cox regression analysis with correction for multiple comparisons (Bonferroni) and established clinical trial co-variates (race, age, tumor size, LN status). Toxicity data indicates that 576 patients experienced grade 2-4 neuropathy and 1633 did not. Clinical predictors for neuropathy include age (12.9% increase with each decade; p=0.004) and African American race (HR=2.1; p=4.5 x 10^{-11}). Six SNPs with MAF>5% demonstrate associations with neuropathy ($\rho<5\chi\ 10^{-7}$). These SNPs reside in two genes: RWDD3 and TECTA. A missense SNP in RWDD3 demonstrates % neuropathy at 15 months follow-up: 27% for homozygous wild-type, 40% for heterozygotes, and 60% for homozygous variant (allele dose-effect: HR=1.5; $p=8.5\ \chi\ 10^{-8}$). Multiple other SNPs with MAF<5% were also associated with neuropathy ($p<5x\ 10^{-7}$).

MATERIALS AND METHODS FOR IDENTIFYING PATIENTS SUSCEPTIBLE TO DEVELOPING TAXANE INDUCED NEUROPATHY

PRIORITY CLAIM

[0001] This application claims the benefit of US provisional patent application number 61/436,813 filed on January 27, 2011, which is incorporated herein by reference in its entirety.

FIELD OF THE INVENTION

[0002] This invention relates generally to using genetic analysis to identify patients with a genetic predisposition for developing neuropathy when treated with taxanes such as paclitaxel.

BACKGROUND

[0003] Treatment with taxanes such as paclitaxel have proven to be effective therapies for the treatment of cancers including breast cancer. Despite the excellent outcomes observed in some patients treated with taxanes such as paclitaxel it is not effective in all patients. In some patients, the therapeutic benefits s associated with the use of these compounds may be outweighed by side effects such as neuropathy. Currently, there exists no method for determining which patients will develop neuropathy when treated with a taxane.

[0004] Given the observation that some patients will develop neuropathy while on a taxane and some will not, there is a pressing need for a method to determine which patients will develop this side effect. Some aspects of the invention disclosed herein provide a genetic basis for detecting patients that are at an increased risk for developing neuropathy when treated with taxanes.

BRIEF SUMMARY OF DISCLOSURE

[0005] Some embodiment of the invention include methods for identifying patients that have genetic predisposition to developing certain side effects associated with treatment with taxanes, including, but not limited to taxanes such as paclitaxel or therapeutic compositions that include taxanes. In some embodiments the method of identifying patients

comprises the steps of: analyzing a sample of genetic material from a patient for the presence of at least one SNP selected from the group of SNPs consisting of SEQ ID NO. 1, SEQ ID NO. 2, SEQ ID NO. 3; and identifying a patient as having a heightened risk of developing a condition wherein said patient's DNA includes at least one SNP listed in Table 1.

[0006] In some embodiments of the invention a patient may be identified or otherwise diagnosed as having an increased genetic-based risk for developing and adverse reaction to at least one taxane based therapeutic compounds based on the presence of all of, or of least one of the following SNPs SEQ. ID NOs. 1; 2 and/or 15 in table 1.

[0007] In some embodiments include method of screening patients, comprising the steps of: identifying a patient wherein the genome of the patient includes at least one single-nucleotide polymorphism selected from the group consisting of SEQ ID No. 1, SEQ ID No. 2, SEQ ID No. 3, SEQ ID No. 4, SEQ ID No. 6, and SEQ ID No. 15, wherein said single-nucleotide polymorphism is detected by contacting at least a portion of the patient's genome with at least one probe that preferentially binds to said single-nucleotide polymorphism; and assigning the patient to a group wherein the group comprises patients that have a higher than normal susceptibility to developing neuropathy when the patients are treated with at least one taxane.

[0008] Still other embodiments include systems for identifying patients, comprising: a sample of genetic material from a patient; and a test, wherein the test is conducted on the sample and identifies patients that have least one single-nucleotide polymorphism selected from the group consisting of SEQ ID No. 1, SEQ ID No. 2, SEQ ID No. 3, SEQ ID No. 4, SEQ ID No. 6, and SEQ ID No. 15, and wherein said test includes contacting at least a portion of the sample with at least one probe that preferentially binds to at least one of the afore-mentioned single-nucleotide polymorphisms.

[0009] In some embodiments the method for identifying patients that have a heightened genetic-based risk of developing conditions such as peripheral neuropathy when exposed to at least one taxane further includes the step of recovering a sample of genetic material either DNA or RNA from a patient. In some embodiments the genetic material recovered from the patient is from either a healthy cell, cancerous cell or pre-cancerous cell.

[0010] In some embodiments of the invention the method of identifying the presence of at least one of the SNPs listed in the Sequence Listing section. The SNPs can be identified any means known in the art including, hybridization, PCR, blotting, sequencing, chip or other array based methods or polynucleotide specific chromatography; which results in a detectable signal or change in signal when an SNP or interest is present in a sample.

[0011] In some embodiments the method of identifying patients harbouring at least one of the SNPs listed in Sequence Listing section is at least partially automated. In some embodiments the identification step is accomplished by use of a computing device wherein the device includes at least one central processing unit.

[0012] Some embodiments are methods for screening patients, comprising the steps of identifying a patient wherein the genome of the patient includes the single-nucleotide polymorphism (SNP) rs3756315 SEQ ID No. 1 and/or rs2296308 SEQ ID No. 2, wherein said single-nucleotide polymorphism or polymorphisms are detected by contacting at least a portion of the patient's genome with at least one probe that preferentially binds to said single-nucleotide polymorphism; and assigning the patient to a group wherein the group comprises patients that have a higher than normal susceptibility to developing neuropathy when the patients are treated with at least one taxane. Taxanes for these purposes include compounds such as paclitaxel available under the trade name Taxol which is a registered trademark of Bristol-Myers Squibb. Methods that can be used to detect the presence of a given single-nucleotide polymorphism include contacting a portion of the patients genome with at least on

reagent that will selectively or at least preferential bind to the SNP of interest. Such methods include but are not limited to contacting at least a portion of the patient's genome with a probe such as complimentary strand of nucleic acid or an antibody. These probes may be labelled and/or attached to surface such a bead, column, chip and the like. Still other methods for detecting the presence of the SNP(s) of interest include using the polymerase chain reaction (PCR) or real time PCR, (RT-PCR) using primers suitable for amplifying the SNP(s) of interest.

[0013] In some embodiments the methods may, further include the step of: analyzing a patient's genome in order to identify the presence of single-nucleotide polymorphisms such as rs3756315 SEQ ID No. 1 and/or rs2296308 SEQ ID No. 2. In still other embodiments the methods may further includes the step of first assigning a patient to a racial group before analyzing said patient's genome for the presence ofsingle-nucleotide polymorphisms. Steps for determined the races of a given patient include self-reporting and/or an analysis the patient's genome.

[0014] Still other embodiments include systems for identifying patients, comprising: a sample of genetic material from a patient; and a test, wherein the test is conducted on the sample and identifies the patients that have a certain single-nucleotide polymorphism, wherein the single-nucleotide polymorphism is rs3756315 SEQ ID No. 1 and/or rs2296308 SEQ ID No. 15, wherein the test includes contacting at least a portion of the sample with at least one probe that preferentially binds to said single-nucleotide polymorphism. Some systems further include an assignment of the patient to a group based on the risk that the patient has for developing neuropathy upon treatment with at least one taxane. Some systems include a screen for patient samples based on the race of the patient. Assignment based on race may occur before the patient's genome is tested for the presence of single-nucleotide

polymorphisms. Steps for determined the races of a given patient include self-reporting and/or an analysis the patient's genome.

SEQUENCE LISTING

[0015] **SEQ ID No. 1.** CAAACTTATTTTATGGTATTTTCATG [C/T]CCAGAATTATTGTGGTTAAACTAAA. SNP No. rs3767315, gene RWDD3/TMEM56.

[0016] **SEQ ID No. 2.** GCCCAGTGTGTGACTGTGAAAGAGAA [G/T]TTACTTGAGCAAGCAGAGAGCCTTT; SNP No. rs2296308; gene RWDD3/TMEM56

[0017] **SEQ ID No. 3.** CCACAGTTAACAAAATAAACAAAATT [A/C]TTCGCCCCCGTGGAGCTGTTAGCAA; SNP No. s3753872; gene RWDD3/TMEM56/AK090700.

[0018] **SEQ ID No. 4.** AACCTATTGACAAGAAAATTTTAAAT [A/C]ATAGATTGATGTACTCTTTAATCAA; SNP No. rs6666528; gene RWDD3/TMEM56/AK090700

[0019] **SEQ ID No. 5.** CGCAAGGTTAGTTTGCACTGACTAAT [C/T]TGGCCAGGAAACATAAACCATTATG; SNP No. rs12378305; gene C9orf135.

[0020] **SEQ ID No. 6.** _AATATTATGAACTTGCTTACCTGTCT [A/G]TTTTCCCCCAATACTTCTAAAAATT; SNP No. rs7555339; gene TMEM56-RWDD3.

[0021] **SEQ ID No. 7.** CATAGAGTTCCTTCTCTATTCCCACC [A/G]TTTCACTTGACTTCACTTTTTTTTC; SNP No. rs11140716; gene C9orf135.

[0022] **SEQ ID No. 8.** GTATACTACTGAGAGGAATCAGTCCT [A/G]TTTTTATCCCTTGATTCCTGGACCC; SNP No. rs4949946; gene Downstream of RWDD3.

[0023] **SEQ ID No. 9.** GTCTGGTTATCCATCCGTGGTGTTTG [C/T]GGAGGTTTCACAAATGCATACACAT; SNP No. rs7053177; gene X-Chromosome: No gene in vicinity..

[0024] **SEQ ID No. 10.** ATATGTTTATATGACTTAGTCTTTTC [A/G]TTTGGACCTCACATAATATGTATAT; SNP No. rs12630808; gene Upstream of OTOL1.

[0025] **SEQ ID No. 11.** GAGAATGTAATGATATTTAAATCTTC [A/G]GCACTGACTATGATTAGACAGGATT; SNP No. rs6785300; gene Chromosome 3: No gene in vicinity.

[0026] **SEQ ID No. 12.** GAATGATAATGGATGATCTGAGAGGC [G/T]TCTGAGGATTTAAGTAAATAGGAAT; SNP No. rs7417186; gene Chromosome 1: No gene in vicinity.

[0027] **SEQ ID No. 13.** CTGATTGGAATCTGCTAAGGAGACTG [C/T]GGGAGGAGAGAAACTGGAGCCAGAA; SNP No. rs2098836; gene Chromosome 2: No gene in vicinity.

[0028] **SEQ ID No. 14.** ATATTTGCCATTACAAAAAAAATAAC [A/G]AGGCATAATGGGAGGAAAATTGGCT; SNP No. rs9554485; gene Chr 13: No gene in vicinity.

[0029] **SEQ ID No. 15.** GCGTTAGAATGTGGGATGCCAGCAAT [C/T]GATAAATTTTAGTGTCATGGGGTTG; SNP No. rs1829; gene TECTA: neurosensory hearing.

[0030] **SEQ ID No. 16.** GTGGCCATGGAGTGGTGCAGCCCACA [C/T]GAGGAACACCACACAGTGACAGCCA; SNP No. rs1501576; gene Chr 9: No gene in vicinity.

[0031] **SEQ ID No. 17.** CTCTGTCTAACTATGACAGTGCTGCC [A/G]TTCAGATAAAAGTATTTATGGTGGT; SNP No. rs2176360; gene Chr 1: No gene in vicinity.

[0032] **`SEQ ID No. 18.** CTTCTTGGTATCAATCACTGCATTCC [C/T]TCCTCAAAGGGTTCCCTTCGAATTG; SNP No. rs11928876; gene Chr 3: No gene in vicinity.

[0033] **SEQ ID No. 19.** TCATGTCTTGCAACAACCCTGTGAGG [A/G]CAGTATTAATGCCCCCTTACAGCAG; SNP No. rs13219; gene CACNA2D4.

[0034] **SEQ ID No. 20.** AACTCTGTAAAACACACTTACATTAT

[A/C]GGTTACAGAATGTCACTCTTACCGT; SNP No. rs1044825; gene CACNA2D4.

[0035] **SEQ ID No. 21.** TTCAGGAAATATCGACAGGGCTACAC

[A/G]TGATGTCCCCAAACTGCTGCTATTG; SNP No. rs7976790; gene Chr 12: No gene in vicinity.

[0036] **SEQ ID No. 22.** ACATCTTGATCTTTCCTCACTTTTCA

[C/T]GGTCAAAAAAGCTACCATTTGTTGA; SNP No. rs7976790
gene Chr 12: No gene in vicinity

[0037] **SEQ ID No. 23.** CTCAGCTCCATATCCGATGTGTCATC

[G/T]TGGGAAGAGCAGTGTCTTCATGAGG; SNP No. rs16997431; gene RTDR1/GNAZ..

[0038] **SEQ ID No. 24.** GTAACTGCCAGAGGTCCCAGGTGGCC

[C/T]GAGGTGATGCCGGGCGCAGGGAGGG; SNP No. rs3753016; gene C21orf89

[0039] **SEQ ID No. 25.** CAAAAATGTCGCTATAGCCACAAAGG

[A/G]TGTTGAGAATGTGGCATAACAGTAC; SNP No. rs10969013; gene Chr 9: No gene in vicinity..

[0040] **SEQ ID No. 26** CATTTATCCTTATTGCATCATAAAAT

[A/G]AAGCCCACAAAATAGGAAATGAGGC; SNP No. rs10932923; gene Chr 2: No gene in vicinity..

[0041] **SEQ ID No. 27.** AAAGAACTGGTAGCTGCCTCCACTCA

[A/G]TGCAGATTATGATGGATATTGTGGA; SNP No. rs11854411; gene Chr 15: No gene in vicinity.

[0042] **SEQ ID No. 28.** TTGCTAGCCAGCACTGCTCCCTACCC

[A/C]CCACCAACACCCTATCTAATGTACA; SNP No. rs7294540; gene Upstream of CACNA2D4.

[0043] **SEQ ID No. 29.** AGTTGATAAATTTGCCTGAAAGTGCT

[C/G]TACCTGTTTGGGTGGGGATGATAAC; SNP No. rs10744552; gene Upstream of CACNA2D4.

[0044] **SEQ ID No. 30.** GTGTCCTACTCCTCCCTATTAAGGGC

[C/T]GGCACTCCATCTTGCTTCAATATAT; SNP No. rs7060868; gene ARMCX4.

[0045] **SEQ ID No. 31.** TAACTGCTACTCATTGAGTGCCTTCT

[A/G]TAGGCAGCCAGTTTATATGTAATTT; SNP No. rs6963568; gene HDAC9.

[0046] **SEQ ID No. 32.** AAGGTGATCCTTCCAGAGCCATCCCA

[A/C]AAAGTCAGCACTGACATGGGATGCA; SNP No. rs2058111; gene CACNA2D4.

[0047] **SEQ ID No. 33.** GCTGCTTGAATTGTGATAAATGTGCT

[A/G]TTTGATTTTTGGTCCTAGTCATTTA; SNP No. rs10138305; gene NUBPL.

[0048] **SEQ ID No. 34.** TACACATTGAGGAATCTCAACATAAT

[A/C]TGAATTAAAGTCATAGAATCATACA; SNP No. rs2050239; gene Chr 9: No gene in vicinity.

[0049] **SEQ ID No. 35.** GCAGAGCTGAGAGATAAAAATAATGT

[C/T]GAAAGTATTGCAGTCACTTTGGCCC; SNP No. rs10822007; gene ZNF365.

[0050] **SEQ ID No. 36.** CCCCTTTTTTTTTGTTAGTCTCTGTT

[G/T]AATTTTCTGATGAAGATGAAGAAAA; SNP No. rs29688; gene Chr 8: No gene in vicinity.

[0051] **SEQ ID No. 37.** TAGAGGCAGAGTCTCCACCGGAGGGC

[C/T]TTGGGAAACACCTGCAAATGATTCA; SNP No. rs2205181; gene C14orf179/BCYRN1.

[0052] **SEQ ID No. 38.** AAATCTCAATTTAAATATAGGAAAAG

[A/G]GAACTTGGCTTCTAGAGAACAGCAG; SNP No. rs6442271; gene hNB-3/CNTN6.

[0053] **SEQ ID No. 39.** GGGTATTGTCTATTTCTGTTTGATTT

[G/T]CCCTTTTAAAGTAGAAATCAACTTT; SNP No. rs1435703; gene RARB .

[0054] **SEQ ID No. 40.** GCCACACGCCCAGTCTGCCTGGACAC

A/G]AGGTTCTCATGGATGGGGCGCGAGC; SNP No. rs4810865; gene PREX1

[0055] **SEQ ID No. 41.** TTTTGTTCTTTAAAAATAGCTGTTAC

[A/G]CTAGTTTCCTACTGCTATAACAAAT; SNP No. rs5951349; gene ARMCX4.

[0056] **SEQ ID No. 42.** AGTCCAGGGCTCGTCCTCCTGCTTGT

[A/G]GACCCTGGCATTTTACTCTAGTGGA; SNP No. rs9531258; gene DCLK1.

[0057] **SEQ ID No. 43.** CCTCTGTGGATTAGTAATTTGTCGCA

[A/G]TTTTATACCACTGGATGCCATAAAT; SNP No. rs16986417; gene PAK3 (dendritic development).

[0058] **SEQ ID No. 44.** AATGTTCACCAACAGTAAAAAACATC

[A/G]TTTATATGTGCAAGACAAGAGAATG; SNP No. rs7306810; gene ARL1.

[0059] **SEQ ID No. 45.** CTTTGCTTCCTGGCCCACTGCGCTGT

[C/T]CCAGCAGAGCACTGCAGCCTCACAG; SNP No. rs8001225; gene DNAJC5B.

[0060] **SEQ ID No. 46.** TACTGTCTGCAGGTACTTGAGCTTAG

[A/C]ACACTGCCTGGTACATAGTAAGTTA; SNP No. rs8001225; gene DCLK1/ MIR548F5.

[0061] **SEQ ID No. 47.** TCTCATTCTTCAACACAAAAACACTT

[G/T]GAGAGTTGTATAAAAGATTTGAAAA; SNP No. rs6043442; gene MACROD2 (hit in GWAS for ALS).

[0062] **SEQ ID No. 48.** GGATTCAAGACATAAATGCTATATAC

[A/G]TGACTATTTTGAATTTTCTATTCAG; SNP No. rs655024; gene FLT1.

[0063] **SEQ ID No. 49.** AGTGGGCAGTTGTGAGAATGAGGCAC

[A/G]ATGGGGAGGACAGCAAGGGGCAGAG; SNP No. rs11832738; gene CACNA1C.

[0064] **SEQ ID No. 50.** TGCTCGAGGTCACACAGCTAGCAAGG

[A/G]GGCATGGTTGCAACCCTATCCAGCT; SNP No. rs134740; gene MIR1301-2/Upstream of SEZ6L.

[0065] **SEQ ID No. 51.** GTATTATTACATGAAACGCTACAGCA

[C/G]ATTAGCAGACAAATGCCAAACTGGC; SNP No. rs10507131; gene ARL1.

[0066] **SEQ ID No. 52.** TCTCTATTAAAAATAAGGCTTCCAGA

[C/T]TGAATGACAAACCTAAAATATGAAG; SNP No. rs7733098; gene ADAMTS19.

[0067] **SEQ ID No. 53.** CTTTAAACAACTGTTATTATAATAAC

[C/T]TGATGCTAAGTAAGGAGACACAATC; SNP No. rs16986428; gene PAK3.

[0068] **SEQ ID No. 54.** GGGTGTTTTTTAGGGTGATGAAAACA

[C/T]GCTGGAATTAGTGATGATGGTTACA; SNP No. rs12250660; gene Chr 10: No Gene in vicinity.

[0069] **SEQ ID No. 55.** TTTTTTTGGTCATCAGGATTTTCTCA

[C/T]TTCAGCCTGTCTTTGATACTGATTT; SNP No. rs7438159; gene Chr 4: No gene in vicinity.

[0070] **SEQ ID No. 56.** AGGCCCTTTGCATGTAGACTCACCTC

[G/T]TTCCCAGCTTCTGATCCTGCCTCTC; SNP No. rs6746015; gene Upstream of RUFY4.

[0071] **SEQ ID No. 57.** GTTGACCACCCCATGTTTGCATTTGC

[C/T]TCTGTTATGGTGTGTTCACATCCCT; SNP No. rs6623268; gene POF1B.

[0072] **SEQ ID No. 58.** ATTCATCATCAGGTGCCTCTCCCCCA

[A/G]GTAGCATTTAAAGCACTCCACAATC; SNP No. rs6664353; gene Upstream LAMC1.

[0073] **SEQ ID No. 59.** TCCCTTCCTCCCTGCAATATCTGCCC

[A/G]TCAAATTTGCACTATTTATTTAAGA; SNP No. rs6664558; gene Chr 1: No gene in vicinity.

[0074] **SEQ ID No. 60.** CTACCAAAAATATTTTTTATGTGAGT

[G/T]CAGTAAGAAACTGTTTCAGATTAAG; SNP No. rs10779162; gene Chr 12: No gene in vicinity.

BRIEF DESCRIPTION OF THE FIGURES

[0075] **FIG. 1.** Kaplan-Meier curves for time to first neuropathy stratified by African-American and other races.

[0076] **FIG. 2.** Kaplan-Meier curves for time to first neuropathy stratified by the treatment arms in the trial E#5103.

[0077] **FIG. 3.** Plot of principle components of race using the Eigenstrat software.

[0078] **FIG. 4.** Manhattan plot of time to develop first neuropathy using the additive model.

[0079] **FIG. 5.** Plot of linkage disequilibrium, recombination rate, and statistical significance of a set of SNPs on Chromosome 1 associated with time to first neuropathy.

[0080] **FIG. 6.** Plot of % of patients as a function of time to first neuropathy for the RWDD3 SNP (rs2296308).

[0081] **FIG. 7.** Manhattan plot of time to develop first neuropathy using the Recessive model.

[0082] **FIG. 8.** Volcano plot of –log10(p values) of SNPs associated with time to first neuropathy using a recessive model plotted as a function of $\log_2$ (Hazard Ratio) effect size.

[0083] **FIG. 9.** Plot of % of patients as function of time to first neuropathy the TECTA SNP (rs1829).

DESCRIPTION

[0084] For the purposes of promoting an understanding of the principles of the novel technology, reference will now be made to the preferred embodiments thereof, and specific language will be used to describe the same. It will nevertheless be understood that no limitation of the scope of the novel technology is thereby intended, such alterations, modifications, and further applications of the principles of the novel technology being contemplated as would normally occur to one skilled in the art to which the novel technology relates.

[0085] One very effective method of treating many cancerous tumors is compounds that target rapidly proliferating cells. Some of these compounds are diterpenes, which can be isolated from the pacific yew tree (*Taxus brevifolia*). These compounds and derivatives thereof are sometimes referred to as taxanes. Some taxanes exhibit clinical utility in the treatment of some cancers, including, Karposi's sacrcoma and cancers of head, neck, breast, lung and ovaries. These compounds have also been used to prevent restenosis and are added to some drug eluting stents to inhibit pathological thickening of the vascular wall following the implantation of a stent. Taxanes that have found utility as drugs for the condition above include paclitaxel (2α,4α,5β,7β,10β,13α)-4,10-bis(acetyloxy)-13-{[(2*R*,3*S*)-3-(benzoylamino)-2-hydroxy-3-phenylpropanoyl]oxy}-1,7-dihydroxy-9-oxo-5,20-epoxytax-11-en-2-yl benzoate) also marketed under the trade name Taxol. These compounds are thought

to interfere with cell division by inhibiting micro-tubual formation in dividing cells, resulting in inhibition of tumor growth.

[0086] This class of compounds is still under intense study and these compounds and/or derivatives thereof may prove to have efficacy against still more diseases and conditions. One recent development in this area is the addition of the monoclonal antibody, bevacizumab to a therapeutic regime that includes taxanes such as paclitaxel. Concurrent and sequential treatment with these drugs holds the promise of effectively treating patients that do not respond well to treatment without this combination of drugs. Increasing the number of patients that can *potentially* benefit from treatment with taxanes also has the potential to increase the number of patients that may suffer from side effects induced by exposure to these compounds.

[0087] Unfortunately, many patients do not respond well to treatment with taxanes or even to treatment with taxanes in combination with other therapeutic agents. Many patients also develop severe side effects when treated with taxanes. One of the most severe side effects noted in many patients treated with, for example, the taxanes paclitaxel, is peripheral neuropathy. Peripheral neuropathy is one of the *most* common toxicities associated with the therapeutic use of taxanes. This toxicity frequently interferes with function and is occasionally irreversible. The only well-established predictors for increased risk of neuropathy include advanced age, history of diabetes, type of taxane, dose of taxane, and schedule of taxane. No biomarkers have been validated to predict which patients might be at greatest risk for this toxicity.

[0088] Various attempts have been made to try and identify bio-markers that can be used to identify patients that are likely to benefit from treatment with taxanes such as paclitaxel. Attempts have also been made to try and identify markers that can help predict which patients are at an increased risk for developing particularly severe side effects such as

peripheral neuropathy when treated with these drugs. Currently, there are no approved diagnostic tests that are able to reliably identify patients that should not be treated with this class of drugs.

[0089] As is often the case when trying to use genomic analysis to predict drug efficacy and side effect severity in specific patients, no correspondence has been established between a single genetic maker diagnostic of both the taxanes' efficacy and their ability to induce peripheral neuropathy. Indeed, it may well be that wholly different genes account for the same patient's propensity to respond to treatment with paclitaxel and their propensity to develop severe peripheral neuropathy.

[0090] A genome-wide association study (GWAS) comparing the genotypes of patients diagnosed with early stage breast cancer and treated with the taxane paclitaxel with and without the co-treatment with bevacizumab with the development of peripheral neuropathy is under way. As reported herein, this GWAS has already identified some genetic variations that help predict which patients are at the greatest risk for developing peripheral neuropathy when they are treated with the taxane paclitaxel.

[0091] Interim toxicity data from this GWAS demonstrated that 576 number of patients experienced grade 2-4 neuropathy and 1633 number of patients did not. Clinical predictors for neuropathy in this study included advanced age ($p=0.004$) and African American race ($p=4.5 \times 10^{-11}$).

[0092] A randomized phase III trial comparing a standard backbone of adjuvant chemotherapy with the same chemotherapy plus concurrent bevacizumab and with concurrent and sequential bevacizumab is underway. The chemotherapy includes 4 cycles of doxorubicin and cyclophosphamide followed by weekly treatment with paclitaxel for 12 weeks. The clinical trial has planned accrual (n=4950). A GWAS is planned for the first 2209 patients to compare genotypes with candidate efficacy and toxicity variables. The

phenotype for this study is grade 2-4 neuropathy. GWAS is conducted using the Infinium HumanOmni1 platform from Illumina (San Diego, CA) which assessed 1.2 million SNPs. The genotype calls have undergone quality control assessments and comparisons were made using Cox regression and chi-square analysis with correction for multiple comparisons. Genome-wide significance included associations with p-values $<10^{-7}$. Three SNPs have been identified as such. Experimental findings will be validated with final patient results being utilized in a clinical assay.

Experimental and Results

[0093] GWAS was performed with DNA derived from blood of patients by using Infinium HumanOmni1 platform from Illumina. The platform allowed for the assessment of over 1.2 million markers to interrogate human genetic variations. The genotyping data underwent quality control (QC) assessment and was statistically correlated with clinical toxicity (neuropathy) data. Significant SNPs for neuropathy were identified with statistical approach. SNP Quality Control (QC) was performed to remove both samples and markers which were deemed to be unreliable. Any samples or SNPs missing > 5% of the genotypic data were removed from further analysis. Samples with excess heterozygosity (indicative of contamination) were excluded. Identity-by-state (IBS) sharing between all pairs of individuals was examined to identify (and delete) duplicates or closely-related individuals. SNPs violating Hardy-Weinberg equilibrium ($p \leq 0.00001$) were discarded. The cluster plots for any SNPs showing evidence of association were visually inspected to ensure that the clusters were sufficiently separated as to render the genotype calls reliable. PLINK (an open source tool set available through Massachusetts General Hospital and the Broad Institute of Harvard University and MIT) was used to an open source toolset generate both per sample and per SNP metrics. Outlier SNPs were reviewed and if necessary, were removed. Statistical analysis was performed for association between the SNPs identified and time to

neuropathy. Important covariates in this analysis were include age and race. A logistic regression was used to analyze these associations. The genetic model implemented studied the gene-dose effect on the genotype relative risk: GRR = P(NE|DD)/P(NE|Dd) = P(NE|Dd)/P(NE|dd) =1.5, where "D" represents the common allele and "d" represents the minor allele. The data analyses were implemented in R function. The per-comparison p-value threshold is 0.05/1200000 ($< 10^{-7}$).

[0094] E5103 is a Phase III clinical trial of lymph node positive or lymph node negative/high risk, HER-2 negative breast cancer patients. In E5103, 4950 patients were randomized to standard adjuvant chemotherapy versus standard adjuvant chemotherapy plus concurrent bevacizumab versus standard adjuvant chemotherapy plus concurrent bevacizumab followed by maintenance bevacizumab. In this trial, standard adjuvant chemotherapy consists of the drugs Doxorubicin and Cyclophosphamide followed by Paclitaxel.

[0095] Referring now to **FIG. 1**. A Kaplan-Meier curve of patients stratified by African-American race compared to all others races demonstrating a significantly quicker time to development of neuropathy in E5103 ($p=2.3x10^{-11}$). This analysis utilized clinical data from E5103 that annotated the length of time from randomization on trial to the development of neuropathy. This data supported the use of race as a statistical covariate. The statistical analysis employed in this analysis was a cox regression.

[0096] Referring now to **FIG. 2**. A Kaplan-Meier curve of the time to first neuropathy of patients enrolled in E5103 stratified by treatment arm. The analysis demonstrated no significant difference in neuropathy between the arms (p=0.18), and thus treatment arm was not used as a statistical covariate. The statistical analysis employed in this analysis was a cox regression.

[0097] Referring now to **FIG. 3**. A principal component analysis of the GWAS SNP data using the Eigenstrat software to genetically determine the race of each patient. As self reported race can sometimes be erroneous in large trials, it is standard practice to determine the race using SNP data, and then use this assignment when doing race based statistical analyses. Because race has been shown to be associated with neuropathy, SNP determined race was used as a covariate in the statistical analyses.

[0098] Referring now to **FIG. 4**. A Manhattan plot of all SNPs tested in the GWAS of E5103. Each dot represents an individual SNP that was genotyped on the GWAS platform. The x-axis represents all the chromosomes of the genome, the y-axis is the $-1\log_{10}$(p-value) of the association between each SNP and time to neuropathy using an additive statistical model. This plot demonstrates SNPs on Chromosome 1 that map to the RWDD3 gene as significantly associated with time to neuropathy (top p-value=$6.49\text{x}10^{-8}$).

[0099] Referring now to **FIG. 5**. A map of the region of chromosome 1 where the significant SNPs identified in **FIG. 4** reside. The green bars with associated gene symbols represent the genic region for each gene. The light blue peaks demonstrate the rate of recombination in this region. The red boxes are the individual SNPs that were genotyped in the GWAS. The placement of the red boxes on the y-axis represents the statistical significance of the association between the SNP and time to neuropathy. The shading of the boxes represents the degree of linkage disequilibrium between each SNP and the most significant SNP in this analysis. This analysis demonstrates that several SNPs in this region are associated with neuropathy and that these SNP are in high linkage disequilibrium with each other. This is a common phenomenon of significant SNPs seen in GWAS studies.

[00100] Referring now to **FIG. 6**. A Kaplan-Meier curve plotting the percentage of patients with neuropathy as a function of time. This analysis demonstrates that patients who carry the RWDD3 rs2296308 minor allele are at significantly increased risk of developing

neuropathy with each increase in allele (HR=1.5 (per allele); $p=8.5x10^{-8}$). The statistical analysis employed in this analysis was a cox regression.

[00101] Referring now to **FIG. 7**. A Manhattan plot of all SNPs tested in the GWAS of E5103. Each dot represents an individual SNP that was genotyped on the GWAS platform. The x-axis represents all the chromosomes of the genome, the y-axis is the $-1og_{10}$(p-value) of the association between each SNP and time to neuropathy using an recessive statistical model. Unlike Figure 4 which used an additive model, a recessive model will tend to identify rare SNPs associated with a phenotype. This plot demonstrates several SNPs as significantly associated with time to neuropathy.

[00102] Referring now to **FIG. 8**. A volcano plot of SNPs (Minor Allele Frequency > 5%) from the recessive statistical model where the log_2 hazard ratio is plotted on the x-axis, and the $-log_{10}$ p-value of the association between SNPs and time to neuropathy is plotted on the y-axis. This sort of analysis will form a plot with a "V" shape where SNPs on the left tip of the "V" are the ones that are most associated with decreased risk of neuropathy, and those on right tip of the "V" are the ones most associated with increased risk of neuropathy. This analysis identified a SNP (rs1829) which maps to the TECTA genes as SNP highly associated with time to neuropathy using the recessive model.

[00103] Referring now to **FIG. 9**. A Kaplan-Meier curve plotting the percentage of patients with neuropathy as a function of time. This analysis demonstrates that patients who are homozygous for TECTA rs1829 minor allele are at significantly increased risk of developing neuropathy (HR=2.07; $p=3.15x10^{-7}$). The statistical analysis employed in this analysis was a cox regression.

Table 1.

SNP	Gene	Seq. ID No.	Sequence
rs3767315	RWDD3/TMEM56	1	CAAACTTATTTTATGGTATTTTCATG[C/T] CCAGAATTATTGTGGTTAAACTAAA
rs2296308	RWDD3/TMEM56	2	GCCCAGTGTGTGACTGTGAAAGAGAA[G/T] TTACTTGAGCAAGCAGAGAGCCTTT
rs3753872	RWDD3/TMEM56/AK090700	3	CCACAGTTAACAAAATAAACAAAATT[A/C] TTCGCCCCCGTGGAGCTGTTAGCAA
rs6666528	RWDD3/TMEM56/AK090700	4	AACCTATTGACAAGAAAATTTTAAAT[A/C] ATAGATTGATGTACTCTTTAATCAA
rs12378305	C9orf135	5	CGCAAGGTTAGTTTGCACTGACTAAT[C/T] TGGCCAGGAAACATAAACCATTATG
rs7555339	TMEM56-RWDD3	6	AATATTATGAACTTGCTTACCTGTCT[A/G] TTTTCCCCCAATACTTCTAAAAATT
rs11140716	C9orf135	7	CATAGAGTTCCTTCTCTATTCCCACC[A/G] TTTCACTTGACTTCACTTTTTTTTC
rs4949946	Downstream of RWDD3	8	GTATACTACTGAGAGGAATCAGTCCT[A/G] TTTTTATCCCTTGATTCCTGGACCC
rs7053177	X-Chromosome: No gene in vicinity	9	GTCTGGTTATCCATCCGTGGTGTTTG[C/T] GGAGGTTTCACAAATGCATACACAT
rs12630808	Upstream of OTOL1	10	ATATGTTTATATGACTTAGTCTTTTC[A/G] TTTGGACCTCACATAATATGTATAT
rs6785300	Chromosome 3: No gene in vicinity	11	GAGAATGTAATGATATTTAAATCTTC[A/G] GCACTGACTATGATTAGACAGGATT
rs7417186	Chromosome 1: No gene in vicinity	12	GAATGATAATGGATGATCTGAGAGGC[G/T] TCTGAGGATTTAAGTAAATAGGAAT
rs2098836	Chromosome 2: No gene in vicinity	13	CTGATTGGAATCTGCTAAGGAGACTG[C/T] GGGAGGAGAGAAACTGGAGCCAGAA
rs9554485	Chr 13: No gene in vicinity	14	ATATTTGCCATTACAAAAAAAATAAC[A/G] AGGCATAATGGGAGGAAAATTGGCT
rs1829	TECTA: neurosensory hearing	15	GCGTTAGAATGTGGGATGCCAGCAAT[C/T]

SNP	Gene	Seq. ID No.	Sequence
			GATAAATTTTAGTGTCATGGGGTTG
rs1501576	Chr 9: No gene in vicinity	16	GTGGCCATGGAGTGGTGCAGCCCACA[C/T] GAGGAACACCACACAGTGACAGCCA
rs2176360	Chr 1: No gene in vicinity	17	CTCTGTCTAACTATGACAGTGCTGCC[A/G] TTCAGATAAAAGTATTTATGGTGGT
rs11928876	Chr 3: No gene in vicinity	18	CTTCTTGGTATCAATCACTGCATTCC[C/T] TCCTCAAAGGGTTCCCTTCGAATTG
rs13219	CACNA2D4	19	TCATGTCTTGCAACAACCCTGTGAGG[A/G] CAGTATTAATGCCCCCTTACAGCAG
rs1044825	CACNA2D4	20	AACTCTGTAAAACACACTTACATTAT[A/C] GGTTACAGAATGTCACTCTTACCGT
rs2286379	CACNA2D4	21	TTCAGGAAATATCGACAGGGCTACAC[A/G] TGATGTCCCCAAACTGCTGCTATTG
rs7976790	Chr 12: No gene in vicinity	22	ACATCTTGATCTTTCCTCACTTTTCA[C/T] GGTCAAAAAAGCTACCATTTGTTGA
rs16997431	RTDR1/GNAZ	23	CTCAGCTCCATATCCGATGTGTCATC[G/T] TGGGAAGAGCAGTGTCTTCATGAGG
rs3753016	C21orf89	24	GTAACTGCCAGAGGTCCCAGGTGGCC[C/T] GAGGTGATGCCGGGCGCAGGGAGGG
rs10969013	Chr 9: No gene in vicinity	25	CAAAAATGTCGCTATAGCCACAAAGG[A/G] TGTTGAGAATGTGGCATAACAGTAC
rs10932923	Chr 2: No gene in vicinity	26	CATTTATCCTTATTGCATCATAAAAT[A/G] AAGCCCACAAAATAGGAAATGAGGC
rs11854411	Chr 15: No gene in vicinity	27	AAAGAACTGGTAGCTGCCTCCACTCA[A/G] TGCAGATTATGATGGATATTGTGGA
rs7294540	Upstream of CACNA2D4	28	TTGCTAGCCAGCACTGCTCCCTACCC[A/C] CCACCAACACCCTATCTAATGTACA
rs10744552	Upstream of CACNA2D4	29	AGTTGATAAATTTGCCTGAAAGTGCT[C/G] TACCTGTTTGGGTGGGGATGATAAC
rs7060868	ARMCX4	30	GTGTCCTACTCCTCCCTATTAAGGGC[C/T]

SNP	Gene	Seq. ID No.	Sequence
			GGCACTCCATCTTGCTTCAATATAT
rs6963568	HDAC9	31	TAACTGCTACTCATTGAGTGCCTTCT[A/G] TAGGCAGCCAGTTTATATGTAATTT
rs2058111	CACNA2D4	32	AAGGTGATCCTTCCAGAGCCATCCCA[A/C] AAAGTCAGCACTGACATGGGATGCA
rs10138305	NUBPL	33	GCTGCTTGAATTGTGATAAATGTGCT[A/G] TTTGATTTTTGGTCCTAGTCATTTA
rs2050239	Chr 9: No gene in vicinity	34	TACACATTGAGGAATCTCAACATAAT[A/C] TGAATTAAAGTCATAGAATCATACA
rs10822007	ZNF365	35	GCAGAGCTGAGAGATAAAAATAATGT[C/T] GAAAGTATTGCAGTCACTTTGGCCC
rs29688	Chr 8: No gene in vicinity	36	CCCCTTTTTTTTTGTTAGTCTCTGTT[G/T] AATTTTCTGATGAAGATGAAGAAAA
rs2205181	C14orf179/BCYRN1	37	TAGAGGCAGAGTCTCCACCGGAGGGC[C/T TTGGGAAACACCTGCAAATGATTCA
rs6442271	hNB-3/CNTN6	38	AAATCTCAATTTAAATATAGGAAAAG[A/G] GAACTTGGCTTCTAGAGAACAGCAG
rs1435703	RARB	39	GGGTATTGTCTATTTCTGTTTGATTT[G/T] CCCTTTTAAAGTAGAAATCAACTTT
rs4810865	PREX1	40	GCCACACGCCCAGTCTGCCTGGACAC[A/G AGGTTCTCATGGATGGGGCGCGAGC
rs5951349	ARMCX4	41	TTTTGTTCTTTAAAAATAGCTGTTAC[A/G] CTAGTTTCCTACTGCTATAACAAAT
rs9531258	DCLK1	42	AGTCCAGGGCTCGTCCTCCTGCTTGT[A/G] GACCCTGGCATTTTACTCTAGTGGA
rs16986417	PAK3 (dendritic development)	43	CCTCTGTGGATTAGTAATTTGTCGCA[A/G] TTTTATACCACTGGATGCCATAAAT
rs7306810	ARL1	44	AATGTTCACCAACAGTAAAAAACATC[A/G] TTTATATGTGCAAGACAAGAGAATG
rs13279522	DNAJC5B	45	CTTTGCTTCCTGGCCCACTGCGCTGT[C/T]

SNP	Gene	Seq. ID No.	Sequence
			CCAGCAGAGCACTGCAGCCTCACAG
rs8001225	DCLK1/ MIR548F5	46	TACTGTCTGCAGGTACTTGAGCTTAG[A/C] ACACTGCCTGGTACATAGTAAGTTA
rs6043442	MACROD2 (hit in GWAS for ALS)	47	TCTCATTCTTCAACACAAAAACACTT[G/T] GAGAGTTGTATAAAAGATTTGAAAA
rs655024	FLT1	48	GGATTCAAGACATAAATGCTATATAC[A/G] TGACTATTTTGAATTTTCTATTCAG
rs11832738	CACNA1C	49	AGTGGGCAGTTGTGAGAATGAGGCAC[A/G] ATGGGGAGGACAGCAAGGGGCAGAG
rs134740	MIR1301-2/Upstream of SEZ6L	50	TGCTCGAGGTCACACAGCTAGCAAGG[A/G] GGCATGGTTGCAACCCTATCCAGCT
rs10507131	ARL1	51	GTATTATTACATGAAACGCTACAGCA[C/G] ATTAGCAGACAAATGCCAAACTGGC
rs7733098	ADAMTS19	52	TCTCTATTAAAAATAAGGCTTCCAGA[C/T] TGAATGACAAACCTAAAATATGAAG
rs16986428	PAK3	53	CTTTAAACAACTGTTATTATAATAAC[C/T] TGATGCTAAGTAAGGAGACACAATC
rs12250660	Chr 10: No Gene in vicinity	54	GGGTGTTTTTTAGGGTGATGAAAACA[C/T] GCTGGAATTAGTGATGATGGTTACA
rs7438159	Chr 4: No gene in vicinity	55	TTTTTTTGGTCATCAGGATTTTCTCA[C/T] TTCAGCCTGTCTTTGATACTGATTT
rs6746015	Upstream of RUFY4	56	AGGCCCTTTGCATGTAGACTCACCTC[G/T] TTCCCAGCTTCTGATCCTGCCTCTC
rs6623268	POF1B	57	GTTGACCACCCCATGTTTGCATTTGC[C/T] TCTGTTATGGTGTGTTCACATCCCT
rs6664353	Upstream LAMC1	58	ATTCATCATCAGGTGCCTCTCCCCCA[A/G] GTAGCATTTAAAGCACTCCACAATC
rs6664558	Chr 1: No gene in vicinity	59	TCCCTTCCTCCCTGCAATATCTGCCC[A/G] TCAAATTTGCACTATTTATTTAAGA
rs10779162	Chr 12: No gene in vicinity	60	CTACCAAAAATATTTTTTATGTGAGT[G/T] CAGTAAGAAACTGTTTCAGATTAAG

[00104] While the novel technology has been illustrated and described in detail in the figures and foregoing description, the same is to be considered as illustrative and not restrictive in character, it being understood that only the preferred embodiments have been shown and described and that all changes and modifications that come within the spirit of the novel technology are desired to be protected. As well, while the novel technology was illustrated using specific examples, theoretical arguments, accounts, and illustrations, these illustrations and the accompanying discussion should by no means be interpreted as limiting the technology. All patents, patent applications, and references to texts, scientific treatises, publications, and the like referenced in this application are incorporated herein by reference in their entirety.

CLAIMS

We claim:

1. A method for screening patients, comprising the steps of:

identifying a patient wherein the genome of the patient includes the single-nucleotide polymorphism rs3756315, **SEQ ID No. 1**, wherein said single-nucleotide polymorphism is detected by contacting at least a portion of the patient's genome with at least one probe that preferentially binds to said single-nucleotide polymorphism; and

assigning the patient to a group wherein the group comprises patients that have a higher than normal susceptibility to developing neuropathy when the patients are treated with at least one taxane.

2. The method according to claim 1, further including the step of:

analyzing a patient's genome in order to identify the presence of single-nucleotide polymorphism rs3756315, **SEQ ID No. 1** in the patient's genome.

3. The method according to claim 3, wherein the method further includes the step of first assigning a patient to a racial group before analyzing said patient's genome for the presence of single-nucleotide polymorphism rs3756315, **SEQ ID No. 1**.

4. The method according to claim 3, wherein the patient's race is determined by self reporting.

5. The method according to claim 3, wherein the patient's race is determined by analyzing the patient's genome.

6. A method for screening patients, comprising the steps of:

identifying a patient wherein the genome of the patient includes the single-nucleotide polymorphism rs3756315 rs2296308, **SEQ ID No. 15**, wherein said single-nucleotide polymorphism is detected by contacting at least a portion of the patient's genome with at least one probe that preferentially binds to said single-nucleotide polymorphism; and

assigning the patient to a group wherein the group comprises patients that have a higher than normal susceptibility to developing neuropathy when the patients are treated with at least one taxane.

7. The method according to claim 6, further including the step of:

analyzing a patient's genome in order to identify the presence of single-nucleotide polymorphism rs2296308, **SEQ ID No. 15**. in the patient's genome.

8. The method according to claim 7, wherein the method further includes the step of first assigning a patient to a racial group before analyzing said patient's genome for the presence of single-nucleotide polymorphism rs2296308, **SEQ ID No. 15**.

9. The method according to claim 8, wherein the patient's race is determined by self reporting.

10. The method according to claim 8, wherein the patient's race is determined by analyzing the patient's genome.

11. A system for identifying patients, comprising:

a sample of genetic material from a patient; and

a test, wherein the test is conducted on the sample and identifies the patients that a single-nucleotide polymorphism, wherein the single-nucleotide polymorphism is rs3756315, **SEQ ID No. 1**, wherein said test includes contacting at least a portion of the sample with at least one probe that preferentially binds to said single-nucleotide polymorphism.

12. The system according to claim 11, further including:

an assignment of the patient to a group based on the risk that the patient has for developing neuropathy upon treatment with at least one taxane.

13. The system according to claim 11, including a screen for patient samples based on the race of the patient.

14. The system according to claim 13, wherein the screen includes the patient's own description of race.

15. The system according to claim 13, wherein the screen for race is based on an analysis of the patient's genome.

16. A system for identifying patients, comprising:

a sample of genetic material from a patient; and

a test, wherein the test is conducted on the sample and identifies the patients that a single-nucleotide polymorphism, wherein the single-nucleotide polymorphism is rs2296308, **SEQ ID No. 15**, wherein said test includes contacting at least a portion of the sample with at least one probe that preferentially binds to said single-nucleotide polymorphism.

17. The system according to claim 15, further including:

an assignment of the patient to a group based on the risk that the patient has for developing neuropathy upon treatment with at least one taxane.

18. The system according to claim 15, including a screen for patient samples based on the race of the patient.

19. The system according to claim 17, wherein the screen includes the patient's own description of race.

20. The system according to claim 17, wherein the screen for race is based on an analysis of the patient's genome.

21. A method for screening patients, comprising the steps of:

identifying a patient wherein the genome of the patient includes at least one single-nucleotide polymorphism selected from the group consisting of **SEQ ID No. 1**, **SEQ ID No. 2**, **SEQ ID No. 3**, **SEQ ID No. 4**, **SEQ ID No. 6**, and **SEQ ID No. 15**, wherein said single-nucleotide polymorphism is detected by contacting at least a portion of the patient's genome with at least one probe that preferentially binds to said single-nucleotide polymorphism; and

assigning the patient to a group wherein the group comprises patients that have a higher than normal susceptibility to developing neuropathy when the patients are treated with at least one taxane.

22. A system for identifying patients, comprising:

a sample of genetic material from a patient; and

a test, wherein the test is conducted on the sample and identifies the patients that have least one single-nucleotide polymorphism selected from the group consisting of **SEQ ID No. 1**, **SEQ ID No. 2**, **SEQ ID No. 3**, **SEQ ID No. 4**, **SEQ ID No. 6**, and **SEQ ID No. 15**, wherein said test includes contacting at least a portion of the sample with at least one probe that preferentially binds to said single-nucleotide polymorphism.

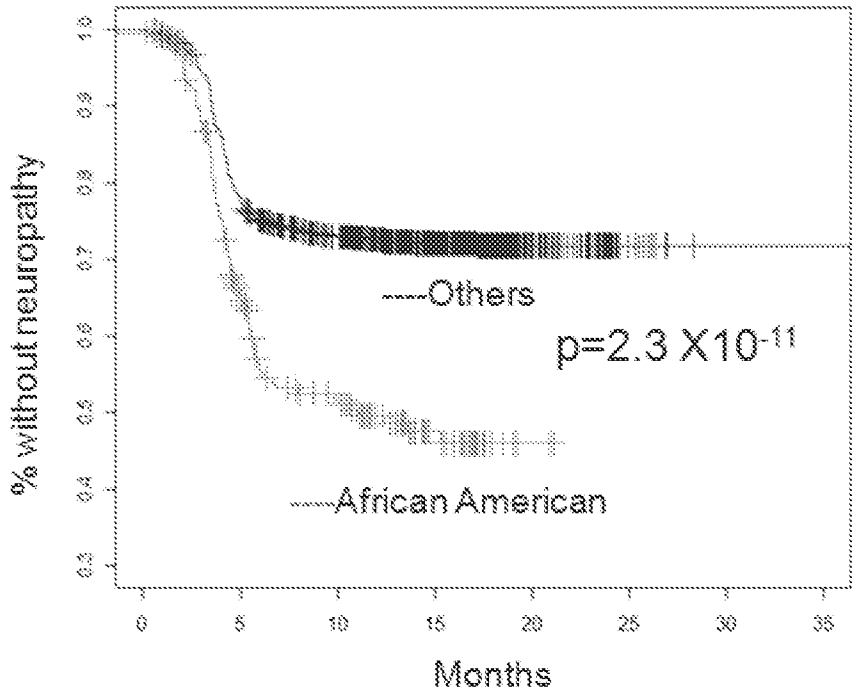
% without neuropathy
1.0
0.9
0.8
0.7
0.6
0.5
0.4
0.3
Others
p=2.3 X10-11
African American
0
5
10
15
20
25
30
35
Months

FIG 1.

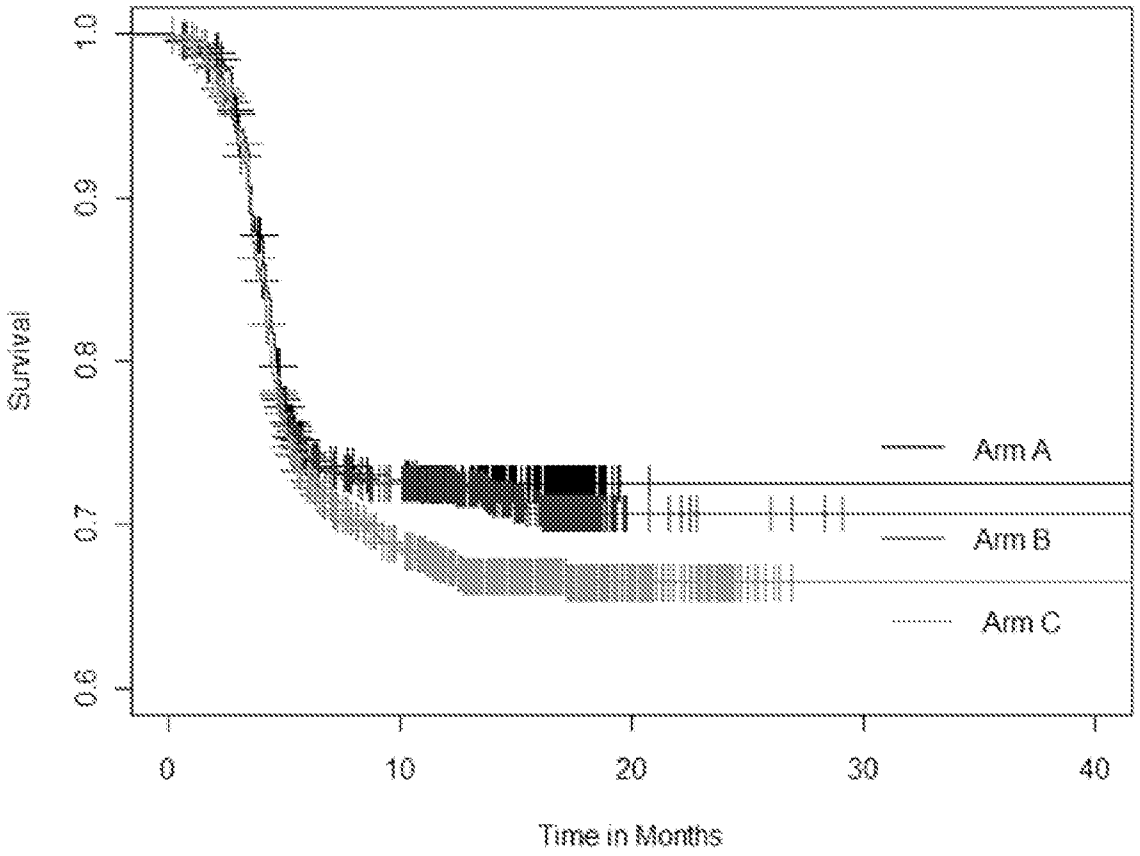
Survival
1.0
0.9
0.8
0.7
0.6
0
10
20
30
40
Time in Months
Arm A
Arm B
Arm C

FIG 2.

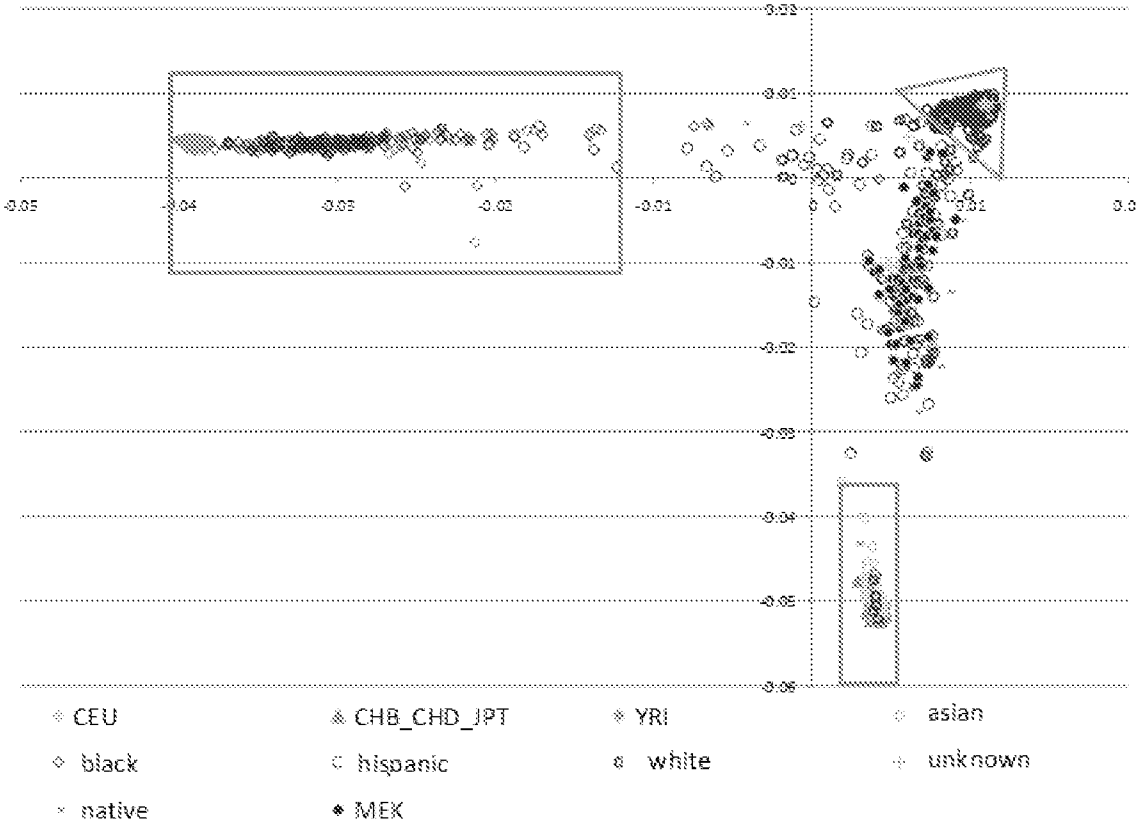
CEU
CHB_CHD_JPT
YRI
asian
black
hispanic
white
unknown
native
MEK

FIG 3.

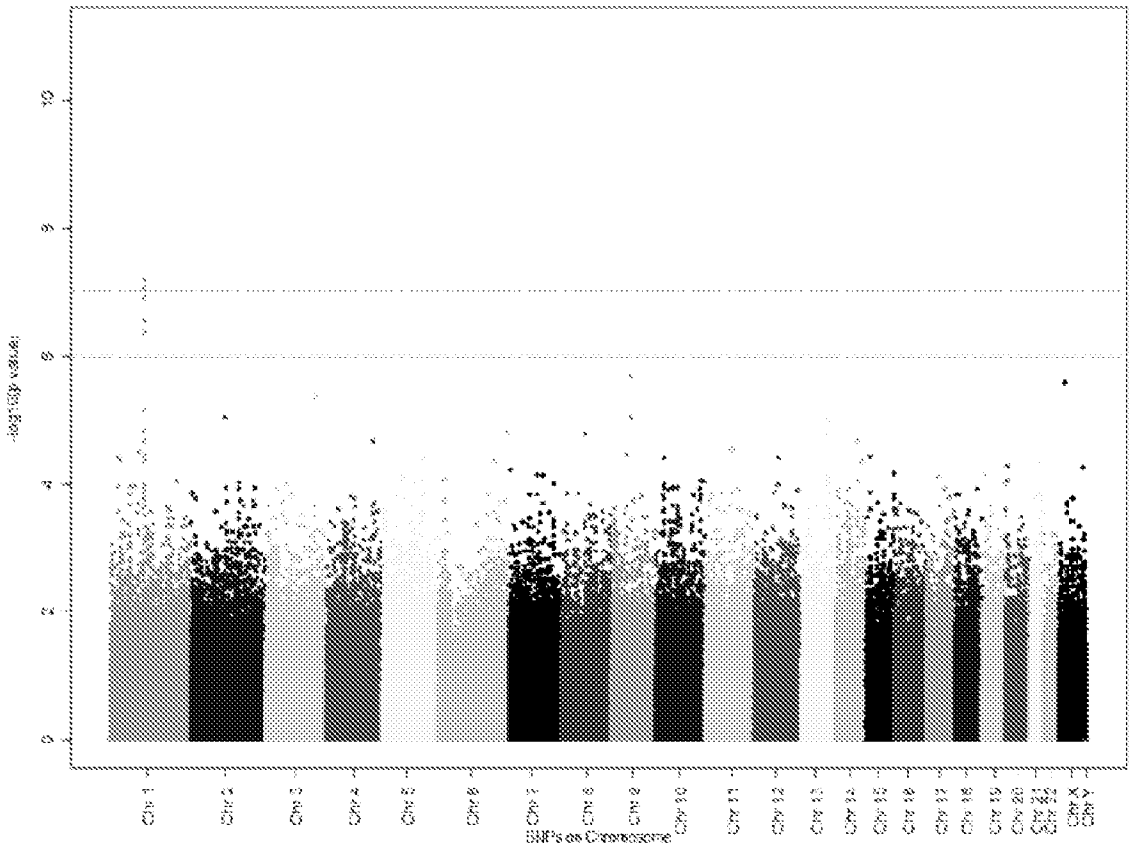

FIG 4.

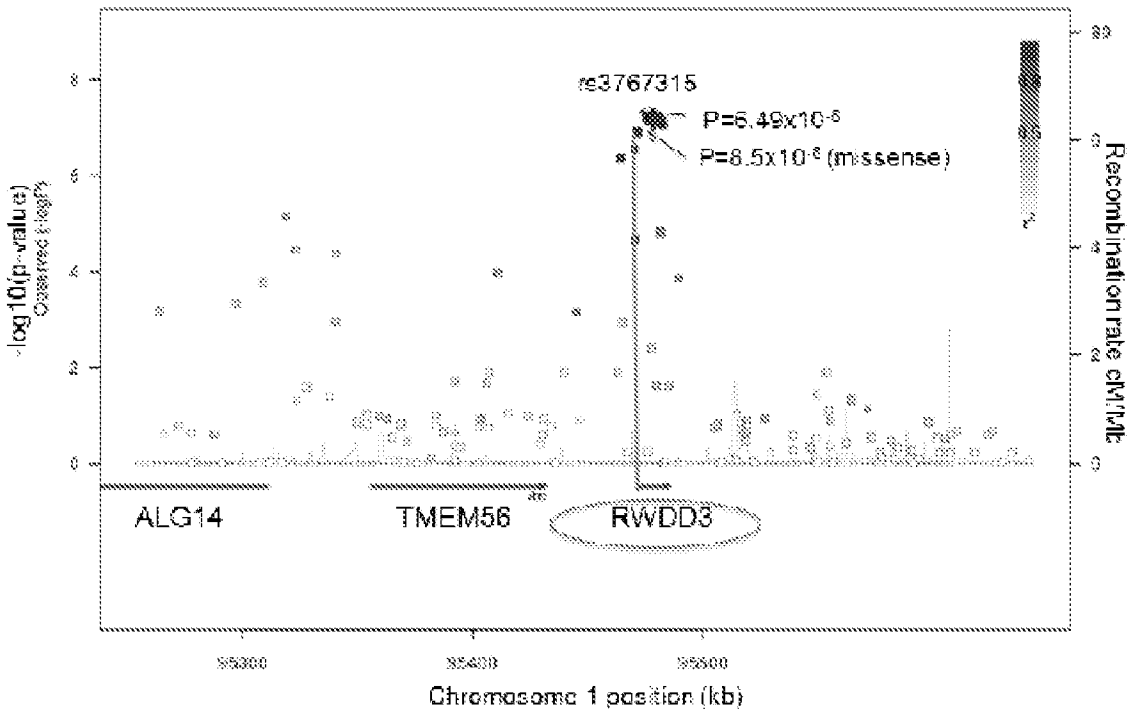
rs3767315
P=6.49x10-6
P=8.5x10-6 (missense)
ALG14
TMEM56
RWDD3
Recombination rate cM/Mb
Chromosome 1 position (kb)

FIG 5.

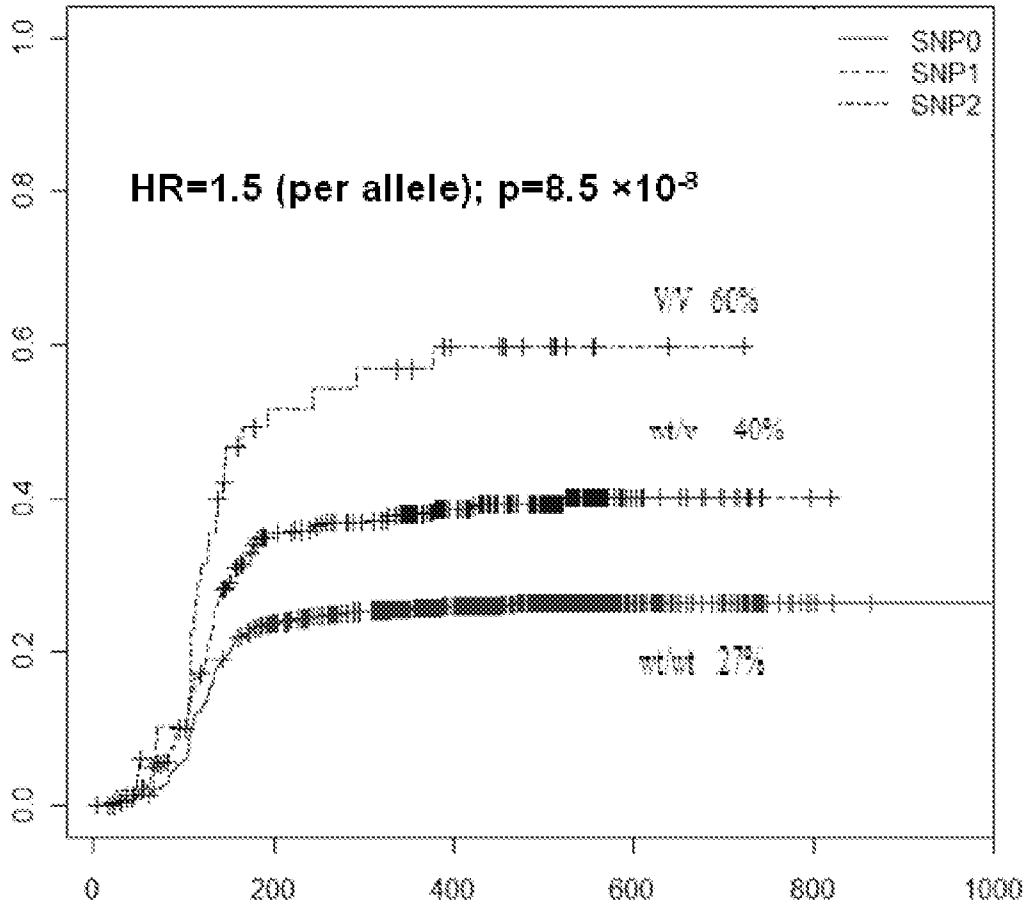
SNP0
SNP1
SNP2
HR=1.5 (per allele); p=8.5 ×10-3
V/V 60%
wt/v 40%
wt/wt 27%
0.0
0.2
0.4
0.6
0.8
1.0
0
200
400
600
800
1000

FIG 6.

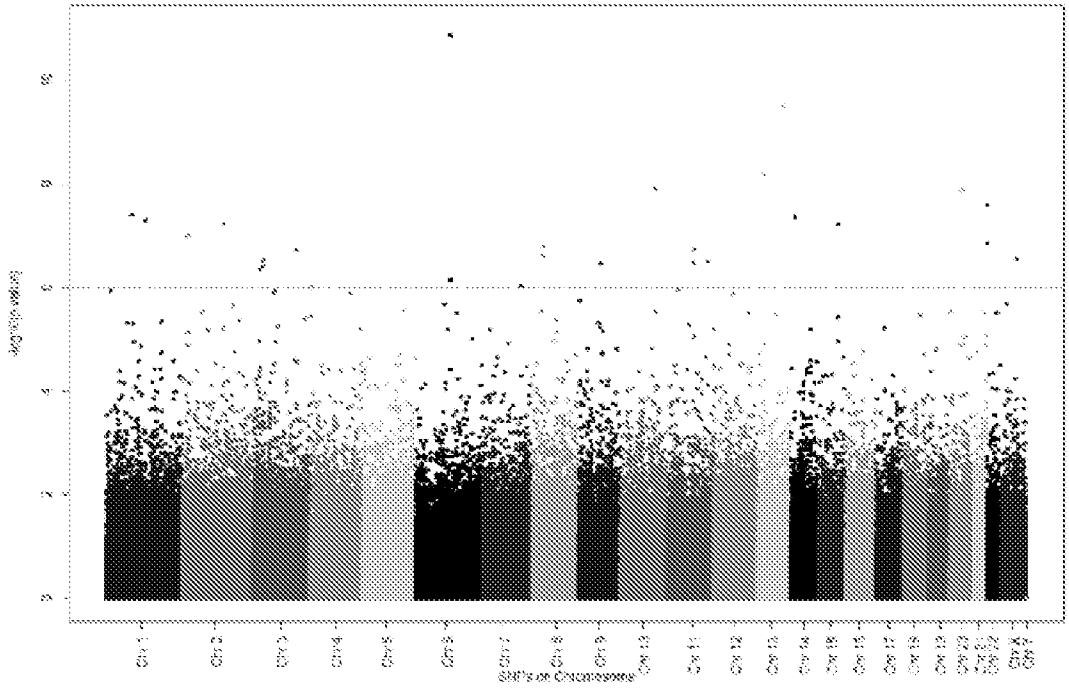

FIG 7.

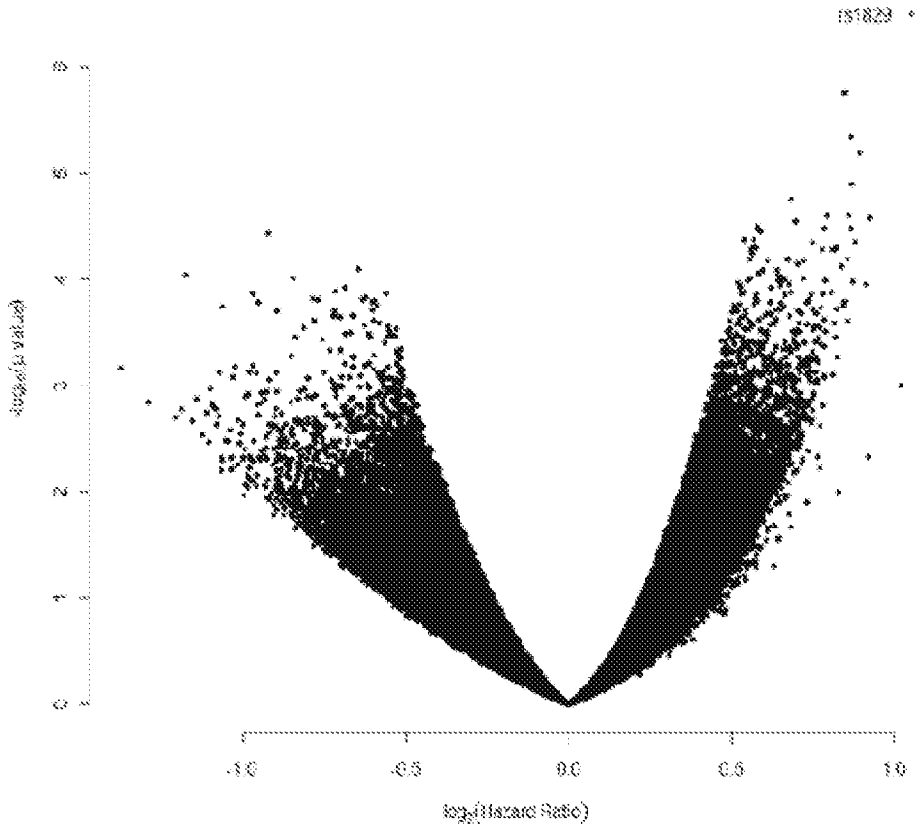

FIG 8.

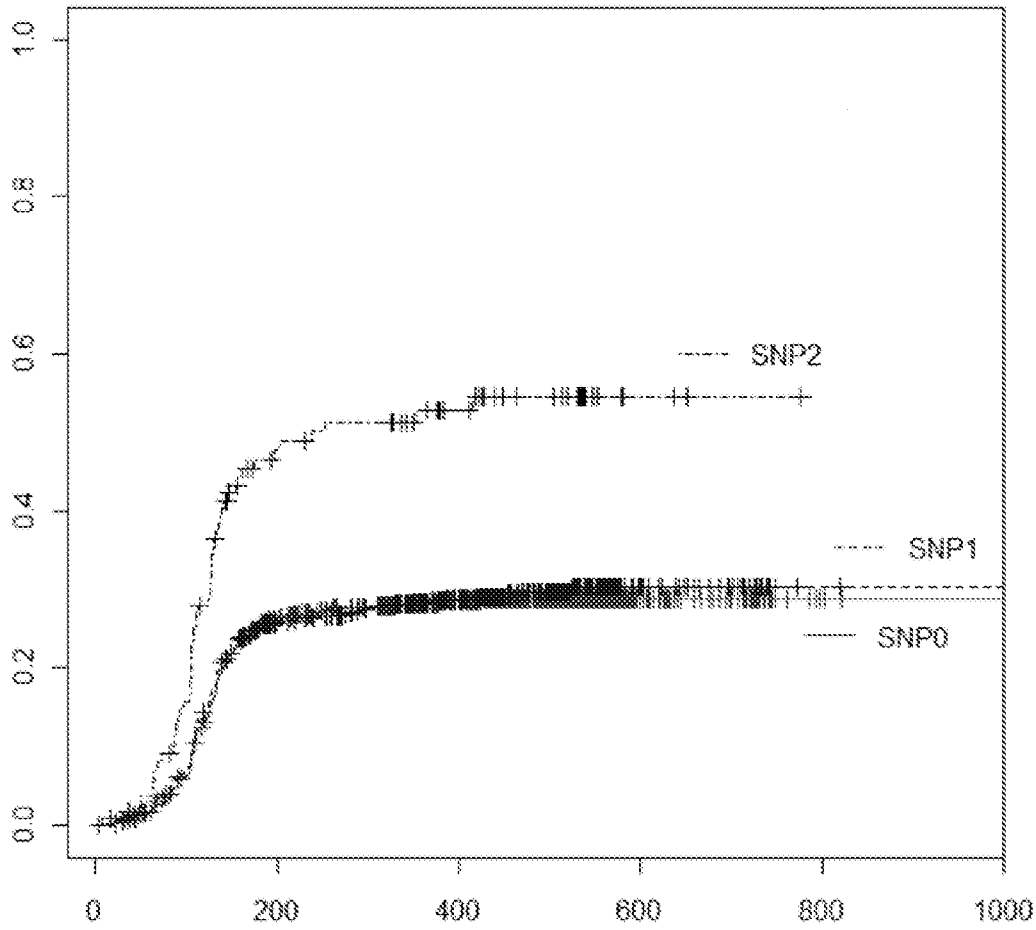

FIG 9.