

(12) INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(19) World Intellectual Property

Organization

International Bureau

(43) International Publication Date

25 March 2021 (25.03.2021)



(10) International Publication Number

WO 2021/055089 A1

(51) International Patent Classification:

C12Q 1/6886 (2018.01)

(21) International Application Number:

PCT/US2020/042503

(22) International Filing Date:

17 July 2020 (17.07.2020)

Published:

— with international search report (Art. 21(3))

(25) Filing Language:

English

(26) Publication Language:

English

(30) Priority Data:

62/903,442

20 September 2019 (20.09.2019) US

(71) Applicants: **THE UNIVERSITY OF NORTH CAROLINA AT CHAPEL HILL** [US/US]; 109 Church Street, Chapel Hill, North Carolina 27516 (US). **DUKE UNIVERSITY** [US/US]; 2812 Erwin Road, Durham, North Carolina 27705 (US).

(72) Inventors: **INNOCENTI, Federico**; c/o The University of North Carolina at Chapel Hill, 109 Church Street, Chapel Hill, North Carolina 27516 (US). **QUINTANILHA, Julia**; c/o The University of North Carolina at Chapel Hill, 109 Church Street, Chapel Hill, North Carolina 27516 (US). **LIN, Danyu**; c/o The University of North Carolina at Chapel Hill, 109 Church Street, Chapel Hill, North Carolina 27516 (US). **OWZAR, Kouros**; c/o Duke University, 2812 Erwin Road, Suite 306, Durham, North Carolina 27705 (US). **WANG, Jin**; c/o The University of North Carolina at Chapel Hill, 109 Church Street, Chapel Hill, North Carolina 27516 (US).

(74) Agent: **MUELLER, Lisa, V.**; Casimir Jones, S.C., 2275 Deming Way, Suite 310, Middleton, Wisconsin 53562 (US).

(81) Designated States (unless otherwise indicated, for every kind of national protection available): AE, AG, AL, AM, AO, AT, AU, AZ, BA, BB, BG, BH, BN, BR, BW, BY, BZ, CA, CH, CL, CN, CO, CR, CU, CZ, DE, DJ, DK, DM, DO, DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, GT, HN, HR, HU, ID, IL, IN, IR, IS, IT, JO, JP, KE, KG, KH, KN, KP, KR, KW, KZ, LA, LC, LK, LR, LS, LU, LY, MA, MD, ME, MG, MK, MN, MW, MX, MY, MZ, NA, NG, NI, NO, NZ, OM, PA, PE, PG, PH, PL, PT, QA, RO, RS, RU, RW, SA, SC, SD, SE, SG, SK, SL, ST, SV, SY, TH, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, WS, ZA, ZM, ZW.

(84) Designated States (unless otherwise indicated, for every kind of regional protection available): ARIPO (BW, GH, GM, KE, LR, LS, MW, MZ, NA, RW, SD, SL, ST, SZ, TZ, UG, ZM, ZW), Eurasian (AM, AZ, BY, KG, KZ, RU, TJ, TM), European (AL, AT, BE, BG, CH, CY, CZ, DE, DK,

(54) Title: METHODS OF IDENTIFYING RISK OF BEVACIZUMAB-INDUCED PROTEINURIA AND HYPERTENSION

(57) Abstract: The disclosure relates to methods of identifying subjects at risk of developing bevacizumab-induced toxicities such as proteinuria and/or hypertension involving measuring nucleic acid or gene mutations in a sample obtained from the subject.



WO 2021/055089 A1

METHODS OF IDENTIFYING RISK OF BEVACIZUMAB-INDUCED PROTEINURIA AND HYPERTENSION

CROSS REFERENCE TO RELATED APPLICATION

[0001] This application claims priority to U.S. Provisional Application No. 62/903,442, filed September 20, 2019, which is hereby incorporated by reference in its entirety.

STATEMENT OF GOVERNMENTAL INTEREST

[0002] This invention was made with government support under grants numbers U10CA180821 and U10CA180882 (to the Alliance for Clinical Trials in Oncology), U24CA196171, UG1CA233253, UG1CA233327, UG1CA233373, R21CA139280-01, and NIH/NCI K07CA140390-01, awarded by the National Cancer Institute. The government has certain rights in the invention.

FIELD

[0003] The present disclosure relates to methods of identifying patients at risk of developing bevacizumab-induced toxicities. In particular, the disclosure relates methods of identifying patients at risk of developing bevacizumab-induced proteinuria and/or hypertension involving measuring nucleic acid mutations in a sample obtained from the patient.

BACKGROUND

[0004] Bevacizumab is a recombinant humanized monoclonal antibody that targets vascular endothelial growth factor (VEGF), inhibiting its binding to its receptors VEGFR1 and VEGFR2. It was approved by the U.S. Food and Drug Administration (FDA) in 2004 and by the European Medicines Agency in 2005 for the treatment of metastatic colorectal cancer. The FDA has also approved its use for the treatment of advanced non-squamous lung cancer, metastatic renal cell carcinoma, recurrent glioblastoma, advanced cervical cancer and platinum-resistant ovarian cancer.¹ Bevacizumab antitumor efficacy relies on its inhibition of the VEGF-signaling pathway involved in endothelial survival, vascular permeability and therefore angiogenesis.²

[0005] Despite the demonstrated efficacy of bevacizumab in combination with other therapies, patients frequently experience toxicity that limits the duration of therapy with bevacizumab and the efficacy of the regimen. The most frequent toxicities are hypertension and proteinuria, with a prevalence that varies in different studies (proteinuria 21%-41%, hypertension 3%-43%).³⁻

⁵ Although hypertension and proteinuria are usually asymptomatic, they can be occasionally life threatening.^{4,5}

[0006] The underlying mechanisms of how bevacizumab induces hypertension and proteinuria are not well understood, but they are postulated to involve nitric oxide (NO) inhibition and increases in peripheral vascular resistance, renal dysfunction and glomerular damage by inhibition of VEGF produced by podocytes. It is not clear whether the occurrence of proteinuria shares the same mechanism responsible for hypertension, or whether the kidney damage is a secondary effect.⁶

[0007] Currently, there are no validated biomarkers to predict bevacizumab-induced hypertension or proteinuria. Previous genetic studies of bevacizumab-induced hypertension focused on a few single-nucleotide polymorphisms (SNPs) in genes of the VEGF pathway.⁷⁻¹⁴

[0008] Despite the reported associations, none of the studies generated robust enough evidence to use these markers in the clinic, mostly because the biomarker signal was not concordant across multiple studies.¹⁶ Accordingly, what is needed are robust biomarkers and methods of identifying patients at risk of bevacizumab-induced hypertension and/or proteinuria that can be reproduced in different studies.

SUMMARY

[0009] Provided herein are methods for determining risk and/or treating a subject.

[0010] In one aspect, provided herein is a method including detecting a mutation in one or more nucleic acids in a sample obtained from a subject who is undergoing therapy or is a candidate for therapy with a VEGF-pathway inhibitor.

[0011] In another aspect, provided herein is a method of predicting the risk of developing one or more VEGF-pathway inhibitor-induced toxicities in a subject, including detecting a mutation in one or more nucleic acids in a sample obtained from the subject who is undergoing therapy or is a candidate for therapy with a VEGF-pathway inhibitor, and determining the risk of developing one or more VEGF-pathway inhibitor-induced toxicities in the subject based upon the presence or absence of the mutation in the one or more nucleic acids in the sample.

[0012] In another aspect, provided herein is a method of treating a subject, comprising detecting a mutation in one or more nucleic acids in a sample obtained from a subject who is undergoing therapy or is a candidate for therapy with a VEGF-pathway inhibitor; determining the risk of developing one or more VEGF-pathway inhibitor-induced toxicities in the subject based upon the presence or absence of the mutation in the one or more nucleic acids in the sample; and modulating therapy with a VEGF-pathway inhibitor and/or providing the subject

with one or more supportive therapies based upon the determined risk of developing one or more VEGF-pathway inhibitor-induced toxicities in the subject.

[0013] In another aspect, provided herein is a method for treating or preventing a VEGF pathway inhibitor-induced toxicity in a subject in need of treatment with a VEGF-pathway inhibitor, the method comprising identifying the subject as having a genetic mutation that confers a risk of developing the VEGF pathway inhibitor-induced toxicity, and treating the subject with a supportive and/or prophylactic therapy for the toxicity in addition to the VEGF-pathway inhibitor.

[0014] In another aspect, provided herein is a method for treating a subject having a disease or disorder, wherein the disease or disorder is indicated for treatment with a VEGF pathway inhibitor, the method comprising identifying the subject as having a genetic mutation that confers a risk of developing a VEGF pathway inhibitor-induced toxicity, treating the subject with a supportive and/or prophylactic therapy to prevent or reduce the toxicity, and treating the subject with the VEGF-pathway inhibitor.

[0015] In embodiments, the mutation is in a gene selected from the group consisting of *KCNAB1*, *DNAH5*, *TRIO*, *RIPK4*, *IL17F*, *ASPH*, *TTMA*, *EPB41L3* and *SLC25A24*. In embodiments, the genetic mutation is a SNP. In embodiments, the genetic mutation is a mutation that lowers expression of *KCNAB1* relative to wild type.

[0016] In embodiments, the SNP is selected from the group consisting of rs339947, rs12482855, rs13135230, rs2350620, rs11662763, rs6770663, rs408130, rs418173, rs12482855, rs444904, and rs427554. In embodiments, the base identified at rs339947 is an adenine, the base identified at rs12482855 is an adenine, the base identified at rs11662763 is an adenine, the base identified at rs408130 is an adenine, the base identified at rs418173 is an adenine, the base identified at rs12482855 is an adenine, the base identified at rs13135230 is an adenine, the base identified at rs11662763 is an adenine, the base identified at rs6770663 is a guanine, the base identified at rs444904 is an adenine, the base identified at rs427554 is an adenine, the base identified at rs2350620 is a guanine, or the base identified at rs11662763 is an adenine. In embodiments, the toxicity comprises hypertension and the SNP is rs677063, wherein the base identified at rs6770663 is a guanine.

[0017] In embodiments, the toxicity comprises hypertension, proteinuria, or both. In embodiments, the methods provided herein comprise administering a prophylactic and/or supportive therapy to prevent or reduce the toxicity. In embodiments, the prophylactic and/or supportive therapy is administered to the patient prior to and/or concurrently with administration of the VEGF pathway inhibitor. In embodiments, the methods comprise

delaying the initiation of treatment with the VEGF pathway inhibitor until the prophylactic and/or supportive therapy has been administered to the subject for at least 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, or more days, and/or until the subject's hypertension or proteinuria or other condition associated with the toxicity is reduced and/or resolved and/or under control. In embodiments, the methods comprise adding one or more prophylactic and/or supportive therapy to the subject's treatment regimen; switching the subject to a different prophylactic and/or supportive therapy; and/or increasing the dose and/or frequency of dosing of an anti-hypertensive agent relative to the dose administered to the subject prior to treatment with the VEGF pathway inhibitor. For example, in embodiments, a subject may have already been undergoing a treatment regimen with a prophylactic and/or supportive therapy for the condition associated with the toxicity risk. In such situations, the methods may comprise adding one or more additional prophylactic and/or supportive therapy, switching to a different class of drug for the prophylactic and/or supportive therapy, switching to a different drug within the same class for the prophylactic and/or supportive therapy, and/or increasing the dose and/or frequency of dosing with the prophylactic and/or supportive therapy, when the subject is identified as being at risk of developing the toxicity upon treatment with a VEGF pathway inhibitor.

[0018] In embodiments, the methods provided herein comprise modulating the dose of the VEGF pathway inhibitor. For example, in embodiments, the methods comprise reducing the total dosing amount, mg/kg dosing amount, or frequency of dosing of the VEGF pathway inhibitor. In embodiments, modulating the dose of the VEGF pathway inhibitor comprises starting at a dose lower than the recommended starting dose and maintaining the low dose or increasing the dose as appropriate with close monitoring for signs of the toxicity. In embodiments, the dose modulation is for the duration of treatment of the VEGF pathway inhibitor. In embodiments, the dose modulation is for a portion of the treatment with the VEGF pathway inhibitor, for example while symptoms of the toxicity persist. In embodiments, the methods comprise monitoring the subject for signs and symptoms of the toxicity or for worsening severity of the toxicity.

[0019] In embodiments, the toxicity comprises hypertension. In embodiments, the methods comprise monitoring the blood pressure of the subject, and/or monitoring the blood pressure of the subject more frequently than the blood pressure would be monitored in a patient who does not have the risk factor for the toxicity as provided herein. In embodiments, the toxicity comprises proteinuria. In embodiments, the toxicity comprises monitoring for proteinuria. In embodiments, monitoring for proteinuria comprises a urine dipstick and sulfosalicyclic acid

test, a 24 hour urine collection test assay, or a spot albumin or protein-to-creatinine ratio test. In embodiments, the prophylactic and/or supportive therapy is an anti-hypertensive agent and/or an agent that treats or prevents proteinuria (e.g., a proteinuria medication). In embodiments, the anti-hypertensive agent or proteinuria medication is selected from the group consisting of loop diuretics, thiazide diuretics, thiazide-like diuretics, potassium-sparing diuretics, calcium channel blockers, ACE inhibitors, angiotensin II receptor antagonists, adrenergic receptor antagonists, vasodilators, renin inhibitors, aldosterone receptor antagonists, alpha-2 adrenergic receptor agonists, and endothelium receptor blockers.

[0020] In embodiments, the VEGF pathway inhibitor is any drug or therapeutic agent that inhibits, interferes with, or alters the VEGF pathway. For example, the VEGF pathway inhibitor may be an antibody, an antibody-like molecule, a small molecule, a soluble protein, a peptide, or the like that interferes with the VEGF-VEGFR interaction. In embodiments, the VEGF pathway inhibitor is selected from the group consisting of bevacizumab, bevacizumab-awwb, bevacizumab-bvzr, ranibizumab, aflibercept, ziv-aflibercept, lenalidomide, lenvatinib, ramucirumab, cabozantinib, pazopanib, sunitinib malate, regorafenib, axitinib, tipiracil and trifluridine, ponatinib, vandetanib, sorafenib, everolimus, thalidomide, temsirolimus, interferon alfa, interferon alfa-2B, interferon alfa-N3, peginterferon alfa-2B, peginterferon alfa-2A, rhEndostatin, cediranib, semaxanib, pomalidomide, alitretinoin, imiquimod, sinecatechins, vismodegib, sonidegib, pegaptanib sodium, dexamethasone intravitreal implant, fluocinolone acetonide, conbercept, brolucizumab-dblb, selpercatinib, nintedanib, apatinib, and motesanib. In embodiments, the VEGF pathway inhibitor is any biosimilar, generic, salt, ester, ether, isomer, mixture of isomers, complex, prodrug, or derivative of any VEGF pathway inhibitor provided herein or otherwise known in the art.

[0021] In embodiments, treating the subject with the VEGF pathway inhibitor comprises reducing exposure of the subject to the VEGF pathway inhibitor relative to the exposure of a subject treated as provided on prescribing information (e.g., the package insert or label) for the VEGF pathway inhibitor. For example, in embodiments, the methods provided herein comprise delaying initiation of treatment with the VEGF inhibitor, reducing the dose of the VEGF inhibitor, reducing the total number of doses of the VEGF inhibitor, reducing the dosing frequency of the VEGF inhibitor, and/or selecting a different VEGF pathway inhibitor (e.g., a VEGF pathway inhibitor that is less likely to be associated with the toxicity) or a non-VEGF pathway inhibitor therapy in the method of treating the subject, wherein the subject has been identified as being at risk of developing the toxicity. In embodiments, reducing the dose of the VEGF inhibitor comprises reducing the dose by about 5%, about 10%, about 25%, about 33%,

about 50%, about 75%, or more relative to a reference dose, wherein the reference dose is the dose provided in prescribing information for the VEGF inhibitor. In embodiments, reducing the total number of doses of the VEGF inhibitor comprises reducing the total number of doses by about 5%, about 10%, about 25%, about 33%, about 50%, about 75%, or more relative to a reference total number of doses, wherein the reference total number of doses are total number of doses provided in prescribing information for the VEGF inhibitor. In embodiments, the methods comprise starting the subject on a lower dose and/or dosing frequency than the starting dose and/or dosing frequency recommended on the package insert for the VEGF pathway inhibitor, and titrating the dose upward to the dose and/or dosing frequency recommended on the package insert. In embodiments, such dosing comprising upward titrating is performed in combination with close monitoring of the subject for the toxicity. In embodiments, reducing the dosing frequency of the VEGF inhibitor comprises reducing the dosing frequency to about one third, about half, or about three quarters as often as the dosing frequency provided in prescribing information for the VEGF inhibitor.

DEFINITIONS

[0022] Unless otherwise defined, all technical and scientific terms used herein have the same meaning as commonly understood by one of ordinary skill in the art. In case of conflict, the present document, including definitions, will control. Preferred methods and materials are described below, although methods and materials similar or equivalent to those described herein can be used in practice or testing of the present disclosure. All publications, patent applications, patents and other references mentioned herein are incorporated by reference in their entirety. The materials, methods, and examples disclosed herein are illustrative only and not intended to be limiting.

[0023] The terms “comprise(s),” “include(s),” “having,” “has,” “can,” “contain(s),” and variants thereof, as used herein, are intended to be open-ended transitional phrases, terms, or words that do not preclude the possibility of additional acts or structures. The singular forms “a,” “and” and “the” include plural references unless the context clearly dictates otherwise. The present disclosure also contemplates other embodiments “comprising,” “consisting of and “consisting essentially of,” the embodiments or elements presented herein, whether explicitly set forth or not.

[0024] For the recitation of numeric ranges herein, each intervening number there between with the same degree of precision is explicitly contemplated. For example, for the range of 6-

9, the numbers 7 and 8 are contemplated in addition to 6 and 9, and for the range 6.0-7.0, the number 6.0, 6.1, 6.2, 6.3, 6.4, 6.5, 6.6, 6.7, 6.8, 6.9, and 7.0 are explicitly contemplated. Recitation of ranges of values herein are merely intended to serve as a shorthand method of referring individually to each separate value falling within the range, unless otherwise indicated herein, and each separate value is incorporated into the specification as if it were individually recited herein. For example, if a concentration range is stated as 1% to 50%, it is intended that values such as 2% to 40%, 10% to 30%, or 1% to 3%, etc., are expressly enumerated in this specification. These are only examples of what is specifically intended, and all possible combinations of numerical values between and including the lowest value and the highest value enumerated are to be considered to be expressly stated in this disclosure.

[0025] The term “single nucleotide polymorphism” or “SNP” as used interchangeably herein refer to a DNA sequence variation occurring when a single nucleotide (adenine (A), thymine (T), cytosine (C), or guanine (G)) in the genome differs between members of a species. Single nucleotides may be changed (substitution), removed (deletions) or added (insertion) to a polynucleotide sequence. Single nucleotide polymorphisms may fall within coding sequences of genes, non-coding regions of genes, or in the intergenic regions between genes. SNPs within a coding sequence may not necessarily change the amino acid sequence of the protein that is produced, due to degeneracy of the genetic code.

[0026] “Subject” and “patient” as used herein interchangeably refers to any vertebrate, including, but not limited to, a mammal (e.g., cow, pig, camel, llama, horse, goat, rabbit, sheep, hamsters, guinea pig, cat, dog, rat, and mouse, a non-human primate (e.g., a monkey, such as a cynomolgus or rhesus monkey, chimpanzee, etc.) and a human). In some embodiments, the subject may be a human or a non-human. In one embodiment, the subject is a human. The subject or patient may be undergoing various forms of treatment, such as with a VEGF-pathway inhibitor. The subject may be male or female. The subject may be of any ancestry. In some embodiments, the subject is of European ancestry.

[0027] “Treat,” “treating” or “treatment” are each used interchangeably herein to describe reversing, alleviating, or inhibiting the progress of a disease and/or injury, or one or more symptoms of such disease, to which such term applies. Depending on the condition of the subject, the term also refers to preventing a disease, and includes preventing the onset of a disease, or preventing the symptoms associated with a disease. A treatment may be either performed in an acute or chronic way. The term also refers to reducing the severity of a disease or symptoms associated with such disease prior to affliction with the disease. Such prevention or reduction of the severity of a disease prior to affliction refers to administration of a treatment

to a subject that is not at the time of administration afflicted with the disease. “Preventing” also refers to preventing the recurrence of a disease or of one or more symptoms associated with such disease.

[0028] “Therapy” and/or “therapy regimen” generally refer to the clinical intervention made in response to a disease, disorder or physiological condition manifested by a patient or to which a patient may be susceptible. The aim of treatment includes the alleviation or prevention of symptoms, slowing or stopping the progression or worsening of a disease, disorder, or condition and/or the remission of the disease, disorder or condition. The term “providing” or “administering” as used herein with relation to a therapy (e.g. a VEGF-pathway inhibitor or a supportive therapy) may refer to providing to the subject the therapy or modulating the dose of a therapy currently being provided to the patient. For example, providing a supportive therapy may refer to increasing the dose of a supportive therapy currently being administered to the subject. The term “supportive therapies” and the like may be used interchangeably herein with “prophylactic therapies” and the like and refers to a therapy other than the therapy with the VEGF pathway inhibitor that prevents or controls (e.g., reduces the severity of or resolves) an adverse event such as hypertension or proteinuria. For example, the supportive therapy may be an anti-hypertensive agent.

DESCRIPTION OF THE DRAWINGS

[0029] These and other features, aspects, and advantages of the present disclosure will become better understood with regard to the following drawings:

[0030] FIG. 1 shows CONSORT and quality control flowchart for CALGB 80303, 40503, 90401, and 40502. *MAF* minor allele frequency, *HWE* Hardy-Weinberg Equilibrium.

[0031] FIG. 2 shows Manhattan plots (left) and quantile-quantile (Q-Q) plots (right) from the SNP-based association results for proteinuria, hypertension, and composite toxicity grade ≥ 2 . Composite toxicity is defined as the occurrence of either proteinuria or hypertension or both.

[0032] FIG. 3 shows effect of genotypes of rs339947 and rs12482855 associated with proteinuria grade ≥ 2 , rs13135230 and rs2350620 associated with hypertension grade ≥ 2 , and rs11662763 associated with composite toxicity grade ≥ 2 . Composite toxicity is defined as the occurrence of either proteinuria or hypertension or both.

[0033] FIG. 4A-4C shows LocusZoom plots using 400 kb window left and right from the variant limits associated with bevacizumab-induced grade ≥ 2 proteinuria (FIG. 4A, top panel and FIG 4C., top panel), composite toxicity (FIG. 4A, bottom panel), and hypertension (FIG. 4B and 4C., bottom panel) in SNP-based analysis. Each circle represents the p-value for one

SNP, with the top SNP shown in purple and the SNPs in the region colored depending on their degree of linkage disequilibrium (LD) (R^2). X-axis denotes the position of the SNP in the region on chromosome; Y-axis denotes the p-value of the association.

[0034] FIG. 5 shows Manhattan plots (left) and quantile-quantile (Q-Q) plots (right) from the SNP-based association results for proteinuria, hypertension, and composite toxicity grade ≥ 3 . Composite toxicity is defined as the occurrence of either proteinuria or hypertension or both.

[0035] FIG. 6 shows LocusZoom plots using 400 kb window left and right from the variant limits associated with bevacizumab-induced grade ≥ 3 proteinuria, hypertension, and composite toxicity in SNP-based analysis. Each circle represents the p-value for one SNP, with the top SNP shown in purple and the SNPs in the region colored depending on their degree of linkage disequilibrium (LD) (R^2). X-axis denotes the position of the SNP in the region on chromosome; Y-axis denotes the p-value of the association.

[0036] FIG. 7 shows quantile-quantile (Q-Q) plot from gene-based association results for grade ≥ 3 proteinuria, hypertension, and composite toxicity. Composite toxicity is defined as the occurrence of either proteinuria or hypertension or both.

[0037] FIG. 8 shows LocusZoom plots using 400 kb window left and right from the *IL17F* and *SLC25A24* limits associated with bevacizumab-induced proteinuria and composite toxicity, respectively, in gene-based analysis of grade ≥ 3 . Each circle represents the p-value for one SNP, with the top SNP shown in purple and the SNPs in the region colored depending on their degree of linkage disequilibrium (LD) (R^2). X-axis denotes the position of the SNP in the region on chromosome; Y-axis denotes the p-value of the association. Composite toxicity is defined as the occurrence of either proteinuria or hypertension or both.

[0038] FIG. 9A provides a quality control flowchart for the TARGET study. Abbreviations: IBS: identical by state, MAF: minor allele frequency, HWE: Hardy-Weinberg Equilibrium, QC: quality control, SNP: single nucleotide polymorphism.

[0039] FIG. 9B is a bar graph showing the frequency of rs444904 AA, GA, and GG genotypes associated with sorafenib-induced hypertension.

[0040] FIG. 10 shows the effect of genotypes of rs427554 associated with bevacizumab-induced hypertension.

[0041] FIG. 11 is a graphic showing the mechanism of action of sorafenib and bevacizumab⁶⁵.

[0042] FIG. 12 is a graphic showing the function of the SP1 transcription factor.⁶⁷ DNMT: DNA methyl transferase.

[0043] FIG. 13 shows the cumulative incidence of grade ≥ 2 hypertension for rs2350620 and rs6770663.

DETAILED DESCRIPTION

[0044] Provided herein are methods of predicting risk and/or treating a subject. In some embodiments, the methods comprise detecting one or more mutations in one or more nucleic acids in a sample obtained from the subject. In some aspects, the methods comprise detecting one or more mutations in one or more genes in a sample obtained from the subject.

[0045] In one aspect, provided herein is a method comprising detecting one or more mutations (e.g., 1, 2, 3, 4, 5, 6, 7, 8, 9 or 10 mutations) in one or more nucleic acids or genes in a sample obtained from a subject. In some embodiments, the method further comprises determining the risk of developing one or more VEGF-pathway inhibitor-induced toxicities in the subject based upon the presence or absence of one or more mutations in the one or more nucleic acids or genes in the sample.

[0046] In another aspect, provided herein is a method of predicting the risk of developing one or more toxicities induced by a therapeutic agent (e.g., a VEGF-pathway inhibitor) in a subject. The method comprises detecting one or more mutations (e.g., 1, 2, 3, 4, 5, 6, 7, 8, 9 or 10 mutations) in one or more nucleic acids or genes in a sample obtained from the subject, and determining the risk of developing one or more VEGF-pathway inhibitor-induced toxicities in the subject based upon the presence or absence of the mutation in the one or more nucleic acids or genes in the sample.

[0047] In another aspect, provided herein is a method of treating a subject comprising detecting one or more mutations in one or more nucleic acids or genes in a sample obtained from a subject, determining the risk of developing one or more VEGF-pathway inhibitor-induced toxicities in the subject based upon the presence or absence of one or more mutations in the one or more nucleic acids or genes in the sample, and modulating therapy with a VEGF-pathway inhibitor based upon the determined risk of developing one or more VEGF-pathway inhibitor-induced toxicities in the subject. Modulating the therapy may include, for example, monitoring the subject for improvement or worsening of the toxicity, administering a supportive therapy to the subject, and/or adjusting the dose of the VEGF-pathway inhibitor. For example, in embodiments, the present disclosure provides methods of treating a subject comprising detecting one or more mutations in one or more nucleic acids or genes in a sample obtained from a subject, determining the risk of hypertension or severe hypertensive crisis in the subject based upon the presence or absence of one or more mutations in the one or more nucleic acids or genes in the sample, and administering to the subject an anti-hypertensive agent prior to or concurrently with administration of the VEGF-pathway inhibitor.

[0048] In another aspect, provided herein is a method of treating a subject, comprising determining the risk of developing one or more VEGF-pathway inhibitor-induced toxicities in the subject based upon the presence or absence of one or more (e.g., 1, 2, 3, 4, 5, 6, 7, 8, 9 or 10 or more mutations) in one or more nucleic acids or genes in a sample obtained from a subject, and modulating therapy with a VEGF-pathway inhibitor based upon the determined risk of developing one or more VEGF-pathway inhibitor-induced toxicities in the subject. In some aspects, the method of treating a subject may be performed by one party. In other aspects, the method of treating a subject may be performed by two or more parties. For example, the presence or absence of one or more mutations in one or more nucleic acids in a sample may be measured by one party and a different party could modulate therapy with a VEGF-pathway inhibitor. For example, one party could analyze the sample to detect one or more mutations in nucleic acids or genes and provide information regarding these mutations to enable a second party to determine the risk in the subject and modulate therapy with the VEGF-pathway inhibitor based upon the determined risk. Alternatively, one party could analyze the sample to detect one or more mutations in nucleic acids or genes and determine the risk of developing one or more VEGF-pathway inhibitor-induced toxicities based upon the analysis, and a second party (e.g. a physician) could then modulate therapy with a VEGF-pathway inhibitor based upon the risk determination provided by the first party.

[0049] In an aspect, provided herein is a method for treating a subject having a disease or disorder associated with neovascularization or angiogenesis, the method comprising identifying the subject as having a mutation in the gene *KCNABI*; treating the subject with an anti-hypertensive agent; and treating the subject with an angiogenesis inhibitor (e.g., a VEGF pathway inhibitor). In embodiments, the mutation is an SNP. In embodiments, the SNP is rs6770663. In embodiments, the base identified at rs6770663 is a guanine. In embodiments, provided herein is a method for treating a population of patients with a VEGF-pathway inhibitor, the method comprising providing a first population of patients who have a disease or disorder indicated for treatment with a VEGF-pathway inhibitor; separating patients who have the SNP rs6770663 into a second population of patients; and treating the second population of patients with an anti-hypertensive agent prior to or concurrently with administering the VEGF pathway inhibitor to the subject.

[0050] In accordance with any of the aspects and embodiments described herein, the subject may be a mammal. In particular embodiments, the subject is a human. The subject may be undergoing treatment or a candidate for treatment with a VEGF-pathway inhibitor.

[0051] Detecting a mutation in one or more nucleic acids in the sample may comprise detecting one or more single-nucleotide polymorphisms (SNPs) in the one or more nucleic acids in the sample, one or more deletions, insertions, copy number variations, inversions, or dislocations; and/or deletion of an entire gene of interest; and/or one or more mutations in one or more genes that affect the expression or function of a gene of interest. In some embodiments, the method comprises detecting a single SNP. In some embodiments, the method comprises detecting two SNPs. In yet other embodiments, the method comprises detecting three SNPs. In other embodiments, the method comprises detecting four SNPs, etc. In some embodiments, one or more SNPs is located in one or more genes provided in Table 8 or Table 9. In embodiments, the mutations provided herein that are associated with the risk of developing a VEGF-pathway-inhibitor-induced toxicity are present in one or more genes selected from the group consisting of *KCNAB1* and *ASPH*.

[0052] *KCNAB1* encodes the K⁺ voltage activated channel subfamily 1 subunit $\beta 1$ (K_v $\beta 1.1$ -1.3) and it is highly expressed in arteries (aorta, coronary, tibial), and endothelial cells. Variant rs6770663 is located in a region of H3K4me1 enhancers in the aorta (see **Table 14**).

[0053] In embodiments, the present disclosure provides mutations that predispose for lower expression of *KCNAB1*. For example, the present disclosure provides methods for treating patients with rs6770663 with a VEGF pathway inhibitor (e.g., bevacizumab), wherein the method comprises modifying the VEGF pathway inhibitor treatment by including monitoring for hypertension, prophylactically treating to prevent hypertension, and/or reducing the dosing level or dosing regimen for the VEGF pathway inhibitor in view of the patient's increased risk of hypertension. Variant rs6770663 has a frequency of about 10% in Europeans and a global frequency of 30%.

[0054] *ASPH* (aspartate β -hydroxylase) encodes the junctin protein which is expressed in arteries and in endothelial cells.

[0055] In some embodiments, the SNP is selected from the SNPs provided in Table 4, Table 5, Table 6, Table 7, Table 10, Table 11, Table 12, Table 13, rs444904, rs427554, or any combinations thereof. For example, one or more SNPs may be selected from the group consisting of rs339947, rs12482855, rs13135230, rs2350620, rs11662763, rs6770663, rs408130, rs418173, rs12482855, rs444904, and rs427554, or any combinations thereof. In some embodiments, a single mutation may be detected. In embodiments, more than one mutation (e.g., 2, 3, 4, 5, 6, 7, 8, 9 or 10 or more mutations) may be detected. For example, multiple SNPs may be evaluated for mutations in the subject. In embodiments, SNP rs6770663 confers susceptibility to VEGF-pathway inhibitor-induced hypertension.

[0056] The present disclosure provides data and validation of the mutations (e.g. SNPs) provided herein as clinically relevant biomarkers of VEGF pathway inhibitor toxicities. For example, the present disclosure demonstrates that mutations provided herein are biomarkers for hypertension and/or proteinuria elicited by more than one different type of VEGF pathway inhibitor. The skilled person will understand that the results provided herein apply to any angiogenesis inhibitor, e.g., any VEGF pathway inhibitor.

[0057] The methods described herein may involve determining the risk of developing one or more VEGF-pathway inhibitor-induced toxicities in the subject. Any suitable toxicity may be evaluated. VEGF inhibitor-induced toxicities include, for example, fatigue, asthenia, weight loss, pain, depression, pyrexia, chills, myalgia, neurologic-sensory neuropathy, gastrointestinal toxicities (e.g. anorexia, decreased appetite, dry mouth, stomatitis, mucositis, nausea, vomiting, diarrhea, constipation, GI perforation), skin toxicities (e.g. HFS, rash, alopecia, depigmentation, pruritus, dry skin, wound healing complications), cardiovascular toxicities (e.g. hypertension, CHF, cardiac ischemia, cerebrovascular ischemia, embolism/thrombosis, bleeding, dyspnea, cough, pneumonitis, dysphonia), myelotoxicities (e.g. anemia, hemoglobin elevation, leukopenia, neutropenia, thrombocytopenia, lymphopenia), metabolic abnormalities (e.g. bilirubin, ALT, AST, gamma-GT abnormalities, INR abnormalities, PTT abnormalities, increased alkaline phosphatase, hypoalbuminemia, lipase elevation, amylase elevation, creatinine increase, increased uric acid, proteinuria, hypophosphatemia, hypothyroidism, increased triglycerides, increased cholesterol, hyperglycemia, hypoglycemia, hypercalcemia, hypocalcemia, hyponatremia), and the like.

[0058] In particular embodiments, VEGF-pathway inhibitor-induced toxicities are selected from proteinuria, hypertension, or both. For example, determining the risk of developing one or more VEGF-pathway inhibitor-induced toxicities may comprise diagnosing the subject as having a high risk of developing proteinuria. In particular embodiments, the subject is diagnosed as having a high risk of developing proteinuria when the base identified at rs339947 is an adenine, the base identified at rs12482855 is an adenine, the base identified at rs11662763 is an adenine, the base identified at rs408130 is an adenine, the base identified at rs418173 is an adenine, or the base identified at rs12482855 is an adenine.

[0059] As another example, determining the risk of developing one or more VEGF-pathway inhibitor-induced toxicities may comprise diagnosing the subject as having a high risk of developing hypertension. In particular embodiments, the subject is diagnosed as having a high risk of developing hypertension when the base identified at rs13135230 is an adenine, the base identified at rs11662763 is an adenine, the base identified at rs6770663 is a guanine, the base

identified at rs444904 is an adenine, or the base identified at rs427554 is an adenine. In embodiments, the subject is determined to be of high risk of developing hypertension when the base identified at rs6770663 is a guanine.

[0060] In some embodiments, determining the risk of developing one or more VEGF-pathway inhibitor-induced toxicities comprises diagnosing the subject as having a low risk of developing hypertension. For example, the subject may be diagnosed as having a low risk of developing hypertension when the base identified at rs2350620 is a guanine.

[0061] In some embodiments, determining the risk of developing one or more VEGF-pathway inhibitor-induced toxicities comprises diagnosing the subject as having a high risk of developing either proteinuria, or hypertension, or both (e.g. composite toxicity). For example, the subject may be diagnosed as having a high risk of developing proteinuria or hypertension or both when the base identified at rs11662763 is an adenine.

[0062] In some embodiments, the methods described herein further comprise modulating therapy with a VEGF-pathway inhibitor based upon the risk determined in the subject. For example, the method may comprise providing the subject with a VEGF-pathway inhibitor or increasing the therapeutic dose of the VEGF pathway inhibitor when the subject is determined to have a low risk of developing one or more VEGF-pathway inhibitor toxicities. For example, the method may comprise providing the subject with a VEGF-pathway inhibitor or increasing the therapeutic dose of the VEGF pathway inhibitor when the subject is diagnosed as having a low risk of developing proteinuria, hypertension, or both. In some embodiments, the method may comprise lowering the dose of a VEGF-pathway inhibitor or ceasing treatment with the VEGF-pathway inhibitor when the subject is determined to have a high risk of developing one or more VEGF-pathway inhibitor toxicities, such as a high risk of developing proteinuria, hypertension, or both. In embodiments, the method may comprise starting the subject who is determined to have a high risk of developing one or more VEGF pathway inhibitor toxicities, such as the high risk of developing proteinuria, hypertension, or both, at a lower dose and/or lower dosing frequency compared to the dose and/or regimen that is recommended on the package insert for the VEGF pathway inhibitor, monitoring the subject for the one or more toxicities, and titrating the dose and/or dosing frequency upwards, if appropriate based on the monitoring for the toxicity.

[0063] In some embodiments, the methods described herein further comprise modulating therapy with or providing the subject with one or more supportive therapies. The term “supportive therapies” refers to a therapy other than the therapy with an anti-cancer agent (e.g. a VEGF pathway inhibitor or other anti-cancer agent). For example, the supportive therapy

may be an anti-hypertensive agent and/or a proteinuria medication. Suitable anti-hypertensive agents and/or proteinuria medications include, for example, diuretics, beta blockers, alpha and beta blockers, calcium channel blockers, angiotensin-converting enzyme (ACE) inhibitors, angiotensin II receptor antagonists (ARBs), adrenergic receptor antagonists, vasodilators (e.g. direct vasodilators), renin inhibitors, aldosterone receptor antagonists, alpha-2 adrenergic receptor agonists, central alpha-2 agonists and other centrally acting drugs, endothelin receptor blockers, and the like.

[0064] In embodiments, if the subject is determined to be at risk of developing one or more VEGF-pathway inhibitor toxicities, the methods provided herein comprise adding a supportive therapy to the subject's treatment regimen, increasing the dose and/or dosing frequency of a supportive therapy that is already a part of the subject's treatment regimen, and/or adding one, two, three, or more additional supportive therapies to the subject's treatment regimen. In embodiments, the added one, two, three or more additional supportive therapies may be different drugs in the same class as one another and/or as a supportive therapy that was already a part of the subject's treatment regimen; or the one, two, three, or more additional supportive therapies may be drugs in a different class as one another and/or as a supportive therapy that was already part of the subject's treatment regimen. Classes of supportive therapies are known in the art and exemplified herein, such as, for example, diuretics, beta blockers, ACE inhibitors, angiotensin II receptor antagonists, calcium channel blockers, direct renin inhibitors, alpha-2 adrenergic receptor agonists, central alpha-2 agonists, and vasodilators.

[0065] Exemplary diuretics may be thiazide or thiazide-type diuretics. For example, the diuretic may be chlorthalidone, hydrochlorothiazide, indapamide, or metolazone. Chlorthalidone or hydrochlorothiazide may be administered, for example, at a dose of about 12.5 to about 50 mg/day, once daily. Indapamide may be administered, for example at a dose of about 1.25 to about 2.5 mg/day, once daily. Metolazone may be administered, for example, at a dose of about 2.5 to about 5 mg/day, once daily. Exemplary diuretics may also be loop diuretics, such as bumetanide, furosemide, or torsemide. Bumetanide may be administered, for example, twice daily at a dose of about 0.5 to about 2 mg/day. Furosemide may be administered, for example, twice daily at a dose of about 20 to about 80 mg/day. Torsemide may be administered, for example, once daily at a dose of about 5 to about 10 mg/day. Exemplary diuretics may also be potassium sparing diuretics, such as amiloride or triamterene. Amiloride may be administered, for example, once or twice daily at a dose of about 5 to about 10 mg/day. Triamterene may be administered, for example, once or twice daily at a dose of about 50 to about 100 mg/day. Exemplary diuretics may also be aldosterone antagonists, such

as eplerenone or spironolactone. Eplerenone may be administered, for example, once or twice daily at a dose of about 50 to about 100 mg/day. Spironolactone may be administered, for example, twice daily at a dose of about 25 to about 100 mg/day. Exemplary diuretics may also include thiazide/potassium-sparing combination diuretics, such as hydrochlorothiazide/triamterene. Hydrochlorothiazide/triamterene may be administered once daily, for example, at a dose of about 25 mg/about 37.5 mg to about 50 mg/about 75 mg.

[0066] Exemplary beta blockers may be cardioselective (e.g., atenolol, betaxolol, bisoprolol, metoprolol (tartate), or metoprolol (succinate) extended release), noncardioselective (e.g., nadolol, propranolol, or long-acting propranolol), cardioselective and vasodilatory (e.g., nebivolol), or intrinsic and sympathomimetic activity beta-blockers (e.g., acebutolol, penbutolol, and pindolol). Atenolol may be administered, for example, once or twice daily at a dose of about 25 to about 100 mg/day. Betaxolol may be administered, for example, once daily at a dose of about 5 to about 20 mg/day. Bisoprolol may be administered, for example, once daily at a dose of about 2.5 mg to about 20 mg/day. Metoprolol (tartate) may be administered once or twice daily at a dose of about 50 to about 200 mg/day. Metoprolol (succinate) extended release may be administered, for example, once daily at a dose of about 50 to about 200 mg/day. Nadolol may be administered, for example, once daily at a dose of about 40 to about 120 mg/day. Propranolol may be administered, for example, twice daily at a dose of about 40 to about 160 mg/day. Long-acting propranolol may be administered, for example, once daily at a dose of about 60 to about 180 mg/day. Nebivolol may be administered, for example, once daily at a dose of about 5 to about 40 mg/day. Acebutolol may be administered, for example, twice daily at a dose of about 200 to about 800 mg/day. Penbutolol may be administered, for example, once daily at a dose of about 10 to about 40 mg/day. Pindolol may be administered, for example, twice daily at a dose of about 10 to about 60 mg/day. Exemplary combined alpha and beta blockers include carvedilol, carvedilol phosphate, and labetalol. Carvedilol may be administered, for example, twice daily at a dose of about 12.5 to about 50 mg/day. Carvedilol phosphate may be administered, for example, once daily at a dose of about 20 to about 80 mg/day. Labetalol may be administered, for example, twice daily at a dose of about 100 mg to about 400 mg/day.

[0067] Exemplary ACE inhibitors include benazepril, captopril, enalapril, fosinopril, lisinopril, moexipril, perindopril, quinapril, ramipril, and trandolapril. Benazepril may be administered, for example, once or twice daily at a dose of about 10 to about 40 mg/day. Captopril may be administered, for example, twice or three times daily at a dose of about 12.5 to about 150 mg/day. Enalapril may be administered, for example, once or twice daily at a dose

of about 5 to about 40 mg/day. Fosinopril may be administered, for example, once daily at a dose of about 10 to about 40 mg/day. Lisinopril may be administered, for example, once daily at a dose of about 5 mg to about 40 mg/day. Moexipril may be administered, for example, once or twice daily at a dose of about 7.5 mg to about 30 mg/day. Perindopril may be administered, for example, once daily at a dose of about 2 to about 16 mg/day. Quinapril may be administered, for example, once or twice daily at a dose of about 10 to about 80 mg/day. Ramipril may be administered, for example, once or twice daily at a dose of about 2.5 to about 20 mg/day. Trandolapril may be administered, for example, once daily at a dose of about 1 to about 4 mg/day.

[0068] Exemplary angiotensin II receptor antagonists include candesartan, eprosartan, irbesartan, losartan, olmesartan, telmisartan, valsartan, and azilsartan. Candesartan may be administered, for example, once daily at a dose of about 8 to about 32 mg/day. Eprosartan may be administered, for example, once or twice daily at a dose of about 400 to about 800 mg/day. Irbesartan may be administered, for example, once daily at a dose of about 150 to about 300 mg/day. Losartan may be administered, for example, once daily at a dose of about 25 to about 100 mg/day. Olmesartan may be administered, for example, once daily at a dose of about 20 to about 40 mg/day. Telmisartan may be administered, for example, once daily at a dose of about 20 to about 80 mg/day. Valsartan may be administered, for example, once or twice daily at a dose of about 80 to about 320 mg/day. Azilsartan may be administered, for example, once daily at a dose of about 40 to about 80 mg/day.

[0069] Exemplary calcium channel blockers may be dihydropyridines (e.g., amlodipine, felodipine, nifedipine long-acting, nisoldipine, isradipine, and nicardipine SR) or nondihydropyridines (e.g., diltiazem ER, verapamil IR, verapamil SR, and verapamil-delayed onset ER). Amlodipine may be administered, for example, once daily at a dose of about 2.5 to about 10 mg/day. Felodipine may be administered, for example, once daily at a dose of about 2.5 to about 20 mg/day. Nifedipine long acting may be administered, for example, once daily at a dose of about 30 to about 90 mg/day. Nisoldipine may be administered, for example, once daily at a dose of about 10 to about 40 mg/day. Isradipine may be administered, for example, twice daily at a dose of about 5 to about 10 mg/day. Nicardipine SR may be administered, for example, twice daily at a dose of about 60 to about 120 mg/day. Diltiazem may be administered, for example, once daily at a dose of about 120 to about 360 mg/day. Verapamil IR may be administered, for example, three times daily at a dose of about 120 to about 360 mg/day. Verapamil SR may be administered, for example, once or twice daily at a dose of about

120 to about 360 mg/day. Verapamil-delayed onset ER may be administered, for example, once daily in the evening at a dose of about 100 to about 300 mg/day.

[0070] An exemplary direct renin inhibitor is aliskiren. Aliskiren may be administered, for example, once daily at a dose of about 150 to about 300 mg/day. Exemplary alpha-1 blockers include doxazosin, prazosin, and terazosin. Doxazosin may be administered, for example, once daily at a dose of about 1 to about 16 mg/day. Prazosin may be administered, for example, two or three times daily at a dose of about 2 to about 20 mg/day. Terazosin may be administered, for example, once or twice daily at a dose of about 1 to about 20 mg/day. Exemplary central alpha2-agonists and other centrally acting drugs include, for example, clonidine oral, clonidine patch, methyldopa, and guanfacine. Clonidine oral may be administered, for example, twice daily at a dose of about 0.1 to about 0.8 mg/day. Clonidine patch may be administered, for example, once weekly at a dose of 0.1 to about 0.3 mg. Methyldopa may be administered, for example, twice daily at a dose of about 250 to about 1000 mg/day. Guanfacine may be administered, for example, once daily at a dose of about 0.5 to about 2 mg/day. Exemplary direct vasodilators include hydralazine and minoxidil. Hydralazine may be administered, for example, two or three times daily at a dose of about 100 to about 200 mg/day. Minoxidil may be administered, for example once, twice, or three times daily at a dose of about 5 to about 100 mg/day.

[0071] In embodiments, any two or more supportive therapies may be used in combination. The skilled person will recognize that the decision of which agents to combine should be based on the complementarity of mechanism of action, evidence of better antihypertensive effect of the combination than either individual agent, and favorable tolerability of the combination. For example, the following combinations of supportive therapies may be used in the methods provided herein: calcium antagonist and ACE inhibitor; calcium antagonist and angiotensin receptor antagonist; calcium antagonist (dihydropyridine) and beta-blocker; calcium antagonist and thiazide diuretic; thiazide diuretic and ACE inhibitor; and thiazide diuretic and angiotensin receptor antagonist.

[0072] In embodiments, a newly added supportive therapy and/or an increased dose of a supportive therapy may be administered prior to treatment with the VEGF-pathway inhibitor. For example, a subject may be identified as having a high risk of developing one or more VEGF-pathway inhibitor toxicities as provided herein, and may be administered a new supportive therapy, and additional supportive therapy, an increased dose of supportive therapy, and/or an increased frequency of dosing of a supportive therapy, for at least 1, at least 2, at least 3, at least 4, at least 5, at least 6, at least 7, at least 8, at least 9, at least 10, at least 11, at

least 12, at least 13, at least 14, or more days before initiation of treatment with the VEGF-pathway inhibitor. In embodiments, the subject is monitored for evidence that the risk of developing one or more VEGF-pathway inhibitor toxicities, or that the likely severity of any such VEGF-pathway inhibitor toxicity, has been reduced prior to initiating therapy with the VEGF-pathway inhibitor. For example, in embodiments, the subject's blood pressure is monitored and the VEGF-pathway inhibitor is withheld until the subject has been determined to be in a safe range for blood pressure.

[0073] In embodiments, a subject has been identified as being at risk of developing one or more VEGF pathway inhibitor toxicities, wherein the subject's blood pressure monitoring is increased prior to, during, or following initiation of therapy with a VEGF pathway inhibitor. In embodiments, increasing blood pressure monitoring may mean increasing the intensity of monitoring. For example, increasing blood pressure monitoring may comprise increasing the frequency of monitoring. For subjects who were not currently monitoring blood pressure regularly, increasing blood pressure monitoring may mean initiating ambulatory blood pressure monitoring, and/or monitoring blood pressure more than once daily, once daily, once every 2, 3, 4, 5, or 6, days, or once weekly. For subjects who were monitoring blood pressure regularly at home, increasing blood pressure monitoring may mean initiating ambulatory blood pressure monitoring where the subject previously only periodically measured blood pressure; or may mean periodic blood pressure monitoring that is performed more often, for example, twice as often. Blood pressure monitoring may be conducted at home by the subject, using single blood pressure measurement devices and/or ambulatory blood pressure monitoring, and/or may be conducted in a hospital or clinic. Ambulatory blood pressure monitoring is blood pressure monitoring using a device that records blood pressure automatically and periodically over a period of time, for example, of 12 hours, 18 hours, 24 hours, 36 hours, 48 hours, or longer.

[0074] In some embodiments, therapy with a VEGF-pathway inhibitor may be modulated and one or more supportive therapies may be provided to the subject based upon the determined risk. For example, the method may comprise lowering the dose of a VEGF-pathway inhibitor and providing a supportive therapy to the subject when the subject is determined to have a high risk of developing one or more VEGF-pathway inhibitor-induced toxicities. In embodiments, lowering the dose of the VEGF pathway inhibitor may comprise starting the subject at a lower dose and/or lower dosing frequency compared to the recommended dose on the package insert for the VEGF pathway inhibitor, and may further comprise monitoring the subject for the toxicity and/or providing a supportive therapy for the toxicity, and titrating the dose and/or dosing frequency upwards as appropriate. In embodiments, the method may comprise lowering

the dose of the VEGF-pathway inhibitor and providing an anti-hypertensive agent or increasing the dose of an anti-hypertensive agent provided to the subject when the subject is determined to have a high risk of developing VEGF-pathway inhibitor-induced hypertension. As another example, the method may comprise lowering the dose of the VEGF-pathway inhibitor and providing a proteinuria medication or increasing the dose of a proteinuria medication provided to the subject when the subject is determined to have a high risk of developing VEGF-pathway inhibitor-induced proteinuria.

[0075] VEGF-pathway inhibitors may be any suitable agent, such as an antibody or a small molecule. VEGF-pathway inhibitors include agents that inhibit any part of the VEGF pathway, including antibodies that bind to VEGF or a VEGF receptor (VEGFR), soluble proteins that bind to or otherwise block interaction of VEGF and VEGFR, small molecule drugs that interfere with the VEGF/VEGFR interaction, and kinase inhibitors. Exemplary VEGF-pathway inhibitors include, without limitation, bevacizumab, bevacizumab-awwb, bevacizumab-bvzr, ranibizumab, aflibercept, ziv-aflibercept, lenalidomide, lenvatinib, ramucirumab, cabozantinib, pazopanib, sunitinib malate, regorafenib, axitinib, tipiracil and trifluridine, ponatinib, vandetanib, sorafenib, everolimus, thalidomide, temsirolimus, interferon alfa, interferon alfa-2B, interferon alfa-N3, peginterferon alfa-2B, peginterferon alfa-2A, rhEndostatin, cediranib, semaxanib, pomalidomide, alitretinoin, imiquimod, sinecatechins, vismodegib, sonidegib, pegaptanib sodium, dexamethasone intravitreal implant, fluocinolone acetonide, conbercept, brovacizumab-dblb, selpercatinib, nintedanib, apatinib, and motesanib. VEGF-pathway inhibitors encompassed by the disclosure also include any biosimilar, generic, salt, ester, ether, isomer, mixture of isomers, complex, prodrug, or derivative of a VEGF-pathway inhibitor. The skilled person will understand how to obtain prescribing information (e.g., information from the product insert or approved label) for VEGF pathway inhibitors; exemplary prescribing information is also provided herein.

[0076] In embodiments, the VEGF-pathway inhibitor is bevacizumab (AVASTIN) or bevacizumab-awwb (MVASI) or bevacizumab-bvzr (ZIRABEV). Bevacizumab is a vascular endothelial growth factor inhibitor indicated for the treatment of metastatic colorectal cancer, in combination with intravenous fluorouracil based chemotherapy for first- or second-line treatment; metastatic colorectal cancer, in combination with fluoropyrimidine-irinotecan- or fluoropyrimidine-oxaliplatin-based chemotherapy for second-line treatment in patients who have progressed on a first-line bevacizumab-containing regimen; unresectable, locally advanced, recurrent or metastatic non-squamous non-small cell lung cancer, in combination with carboplatin and paclitaxel for first-line treatment; recurrent glioblastoma in adults;

metastatic renal cell carcinoma in combination with interferon alfa; persistent, recurrent, or metastatic cervical cancer, in combination with paclitaxel and cisplatin, or paclitaxel and topotecan; and epithelial ovarian, fallopian tube, or primary peritoneal cancer (i) in combination with carboplatin and paclitaxel, followed by bevacizumab as a single agent, for stage III or IV disease following initial surgical resection, (ii) in combination with paclitaxel, pegylated liposomal doxorubicin, or topotecan for platinum-resistant recurrent disease who received no more than 2 prior chemotherapy regimens, and (iii) in combination with carboplatin and paclitaxel or carboplatin and gemcitabine, followed by bevacizumab as a single agent, for platinum sensitive recurrent disease. Bevacizumab is administered intravenously and is provided in dosage forms of 100 mg/4 mL (25 mg/mL) or 400 mg/16 mL (25 mg/mL) in a single-dose vial.

[0077] For metastatic colorectal cancer, bevacizumab is administered at a dose of 5 mg/kg every 2 weeks with bolus-IFL (irinotecan 125 mg/m², fluorouracil 500 mg/m², and leucovorin 20 mg/m² given once weekly for 4 weeks every 6 weeks); 10 mg/kg every 2 weeks with FOLFOX4; or 5 mg/kg every 2 weeks or 7.5 mg/kg every 3 weeks with fluoropyrimidine-irinotecan- or fluoropyrimidine-oxaliplatin-based chemotherapy after progression on a first-line bevacizumab containing regimen. For first-line non-squamous non-small cell lung cancer, bevacizumab is administered at a dose of 15 mg/kg every 3 weeks with carboplatin and paclitaxel. For recurrent glioblastoma, bevacizumab is administered at a dose of 10 mg/kg every 2 weeks. For metastatic renal cell carcinoma, bevacizumab is administered at a dose of 10 mg/kg every 2 weeks with interferon alfa. For persistent, recurrent, or metastatic cervical cancer, bevacizumab is administered at a dose of 15 mg/kg every 3 weeks with paclitaxel and cisplatin, or paclitaxel and topotecan. For stage III or IV epithelial ovarian, fallopian tube or primary peritoneal cancer following initial surgical resection, bevacizumab is administered at a dose of 15 mg/kg every 3 weeks with carboplatin and paclitaxel for up to 6 cycles, followed by 15 mg/kg every 3 weeks as a single agent, for a total of up to 22 cycles. For platinum-resistant recurrent epithelial ovarian, fallopian tube or primary peritoneal cancer, bevacizumab is administered at a dose of 10 mg/kg every 2 weeks with paclitaxel, pegylated liposomal doxorubicin, or topotecan given every week, or 15 mg/kg every 3 weeks with topotecan given every 3 weeks. For platinum-sensitive recurrent epithelial ovarian, fallopian tube, or primary peritoneal cancer, bevacizumab is administered at a dose of 15 mg/kg every 3 weeks with carboplatin and paclitaxel for 6-8 cycles, followed by 15 mg/kg every 3 weeks as a single agent; or 15 mg/kg every 3 weeks with carboplatin and gemcitabine for 6-10 cycles, followed by 15 mg/kg every 3 weeks as a single agent.

[0078] Arterial thromboembolic events, venous thromboembolic events, hypertension, and proteinuria are among the adverse reactions that can occur in patients administered bevacizumab. For hypertension, blood pressure may be monitored and patients may be treated for the hypertension, e.g., with an anti-hypertensive agent; bevacizumab may be withheld if hypertension is not medically controlled. Bevacizumab can be resumed once controlled, but should be discontinued for hypertensive crisis or hypertensive encephalopathy. For renal injury and proteinuria, doctors are instructed to monitor urine protein and to discontinue bevacizumab for nephrotic syndrome, and withhold until less than 2 grams of protein are detectable in urine. Presently, there is no known method for identifying patients at risk of hypertension and/or proteinuria prior to treatment with bevacizumab.

[0079] In embodiments, the VEGF-pathway inhibitor is ranibizumab. Ranibizumab (LUCENTIS) is a vascular endothelial growth factor (VEGF) inhibitor, indicated for the treatment of patients with neovascular (wet) Age-Related Macular Degeneration (AMD), macular edema following retinal vein occlusion (RVO), diabetic macular edema (DME), diabetic retinopathy (DR), and myopic choroidal neovascularization (mCNV). Ranibizumab is for ophthalmic intravitreal injection. For wet AMD, 0.5 mg (0.05 mL) is recommended to be administered by intravitreal injection once a month (approximately 28 days). Although not as effective, patients may be treated with 3 monthly doses followed by less frequent dosing, or may be treated with one dose every 3 months after 4 monthly doses, with regular assessment. For macular edema following RVO, 0.5 mg (0.05 mL) is recommended to be administered by intravitreal injection once a month (approximately 28 days). For DME and DR, .3 mg (0.05 mL) is recommended to be administered by intravitreal injection once a month (approximately 28 days). For mCNV, 0.5 mg (0.05 mL) is recommended to be initially administered by intravitreal injection once a month (approximately 28 days) for up to three months. Patients may be retreated if needed. The dosage forms provided for ranibizumab are single-use prefilled syringe or glass vials containing 10 mg/mL solutions designed to provide 0.05 mL for intravitreal injections; or containing 6 mg/mL solution (0.3 mg). There is a potential risk of arterial thromboembolic events following intravitreal use of VEGF inhibitors.

[0080] In embodiments, the VEGF-pathway inhibitor is aflibercept. Aflibercept (EYLEA) is a vascular endothelial growth factor (VEGF) inhibitor indicated for the treatment of patients with wet AMD, macular edema following RVO, DME, and DR. For wet AMD, the recommended dose is 2 mg (0.05 mL) administered by intravitreal injection every 4 weeks (approximately every 28 days, monthly) for the first 3 months, followed by 2 mg (0.05 mL) via intravitreal injection once every 8 weeks (2 months). Some patients may need every 4 week (monthly)

dosing after the first 12 weeks (3 months). Although not as effective as the recommended every 8 week dosing regimen, patients may also be treated with one dose every 12 weeks after one year of effective therapy. For macular edema following RVO, the recommended dose is 2 mg (0.05 mL) administered by intravitreal injection once every 4 weeks (approximately every 25 days, monthly). For DME and DR, the recommended dose is 2 mg (0.05 mL) administered by intravitreal injection every 4 weeks (approximately every 28 days, monthly) for the first 5 injections followed by 2 mg (0.05 mL) via intravitreal injection once every 8 weeks (2 months). Some patients may need every 4 week (monthly) dosing after the first 20 weeks (5 months). Aflibercept is provided in dosage forms for injection of 2 mg/0.05 mL solution in a single-dose pre-filled syringe or a single-dose vial. As with ranibizumab, there is a potential risk of arterial thromboembolic events following intravitreal use of aflibercept.

[0081] In embodiments, the VEGF-pathway inhibitor is ziv-aflibercept. Ziv-aflibercept (ZALTRAP) is indicated for the treatment of patients with metastatic colorectal cancer that is resistant to or has progressed following an oxaliplatin-containing regimen, a vascular endothelial growth factor inhibitor, in combination with fluorouracil, leucovorin, irinotecan (FOLFIRI). Ziv-aflibercept is administered 4 mg/kg as an intravenous infusion over 1 hour every 2 weeks in combination with FOLFIRI until disease progression or unacceptable toxicity. Ziv-aflibercept is to be administered prior to any component of the FOLFIRI regimen on the day of treatment. Arterial thromboembolic events, hypertension, and proteinuria are among the adverse effects that may be induced by ziv-aflibercept administration. For hypertension, doctors may monitor blood pressure and treat hypertension; may temporarily suspend ziv-aflibercept if hypertension is not controlled (and upon resumption, permanently reduce to 2 mg/kg); and may discontinue it if hypertensive crisis develops. For proteinuria, doctors may monitor urine protein; may suspend ziv-aflibercept for proteinuria of 2 grams per 24 hours or more (to be resumed when proteinuria is less than 2 grams per 24 hours, and then permanently reduce to 2 mg/kg for recurrent proteinuria); and may discontinue it if nephrotic syndrome or thrombotic microangiopathy (TMA) develops. The provided dosage forms of ziv-aflibercept are a 100 mg/4 mL (25 mg/mL) and a 200 mg/8 mL (25 mg/mL) solution in a single-dose vial for injection.

[0082] In embodiments, the VEGF-pathway inhibitor is lenalidomide. Lenalidomide (REVLIMID) is a thalidomide analogue indicated for the treatment of adult patients with multiple myeloma (MM), in combination with dexamethasone (25 mg once daily orally on Days 1-21 of repeated 28-day cycles in combination with dexamethasone); MM, as maintenance following autologous hematopoietic stem cell transplantation (auto-HSCT)

(initiated after therapy after adequate hematologic recovery (ANC at least 1000/mcL and/or platelet counts at least 75,000/mcL, recommended starting dose of 10 mg once daily continuously (Days 1-28 of repeated 28-day cycles) until disease progression or unacceptable toxicity, and after 3 cycles of maintenance therapy, the dose can be increased to 15 mg once daily if tolerated); transfusion-dependent anemia due to low- or intermediate-1-risk myelodysplastic syndromes (MDS) associated with a deletion 5q abnormality with or without additional cytogenetic abnormalities (10 mg once daily); mantle cell lymphoma (MCL) whose disease has relapsed or progressed after two prior therapies, one of which included bortezomib (25 mg once daily orally on Days 1-21 of repeated 28-day cycles); previously treated follicular lymphoma (FL), in combination with a rituximab product (20 mg once daily orally on Days 1-21 of repeated 28-day cycles for up to 12 cycles in combination with a rituximab-product); and previously treated marginal zone lymphoma (MZL), in combination with a rituximab product (20 mg once daily orally on Days 1-21 of repeated 28-day cycles for up to 12 cycles in combination with a rituximab-product). Lenalidomide is provided as 2.5 mg, 5 mg, 10 mg, 15 mg, 20 mg, and 25 mg capsules. There is significantly increased risk of deep vein thrombosis and pulmonary embolism as well as risk of myocardial infarction and stroke in patients receiving REVLIMID with dexamethasone; anti-thrombotic prophylaxis is recommended.

[0083] In embodiments, the VEGF-pathway inhibitor is lenvatinib (LENVIMA). Lenvatinib is a kinase inhibitor that is indicated for the treatment of patients with locally recurrent or metastatic, progressive, radioactive iodine-refractory differentiated thyroid cancer (DTC); combination with everolimus, for the treatment of patients with advanced renal cell carcinoma (RCC) following one prior antiangiogenic therapy; for the first-line treatment of patients with unresectable hepatocellular carcinoma (HCC); and in combination with pembrolizumab, for the treatment of patients with advanced endometrial carcinoma that is not microsatellite instability-high (MSI-H) or mismatch repair deficient (dMMR), who have disease progression following prior systemic therapy and are not candidates for curative surgery or radiation. Lenvatinib is available as 4 mg and 10 mg capsules. Lenvatinib is taken daily at a recommended dosage of 24 mg orally (for DTC), 18 mg orally with 5 mg everolimus (for RTC), and 20 mg orally with 200 mg i.v. pembrolizumab (for endometrial carcinoma). For HCC, the recommended dosage is based on body weight: 12 mg orally once daily for patients greater than or equal to 60 kg and 8 mg orally once daily for patients less than 60 kg. Doses are modified for adverse reactions as follows. For DTC, the first reduction is to 20 mg once daily, the second is to 14 mg once daily, the third is to 10 mg once daily. For RCC and endometrial carcinoma, the first reduction is to 14 mg once daily, the second is to 10 mg once daily, the third is to 8

mg once daily. For HCC patients that weigh 60 kg or more, the first reduction is to 8 mg once daily, the second reduction is to 4 mg once daily, and the third reduction is to 4 mg every other day; and for HCC patients that weight less than 60 kg, the first reduction is to 4 mg once daily, the second reduction is to 4 mg every other day, and the third is to discontinue. Hypertension, cardiac dysfunction, arterial thromboembolic events, and proteinuria are adverse reactions that may occur. For hypertension, blood pressure is monitored during treatment and lenvatinib is withheld for grade 3 hypertension despite optimal antihypertensive therapy. The drug can be resumed at a reduced dose when hypertension is controlled at less than or equal to grade 2. Lenvatinib is discontinued for grade 4 hypertension, grade 4 cardiac dysfunction, an arterial thromboembolic event of any grade, and nephrotic syndrome.

[0084] In embodiments, the VEGF-pathway inhibitor is ramucirumab. Ramucirumab (CYRAMZA) is a VEGFR2 antagonist indicated as a single agent or in combination with paclitaxel, for treatment of advanced or metastatic gastric or gastro-esophageal junction adenocarcinoma with disease progression on or after prior fluoropyrimidine- or platinum-containing chemotherapy; in combination with docetaxel, for treatment of NSCLC with disease progression on or after platinum-based chemotherapy; in combination with FOLFIRI, for the treatment of metastatic colorectal cancer with disease progression on or after prior therapy with bevacizumab, oxaliplatin, and a fluoropyrimidine; and as a single agent, for the treatment of hepatocellular carcinoma in patients who have an alpha fetoprotein of ≥ 400 ng/mL and have been treated with sorafenib. Ramucirumab is for intravenous infusion (first infusion over 60 minutes and if tolerated, all subsequent infusions may be administered over 30 minutes) and is supplied as a mg/10 mL (10 mg/mL) or 500 mg/50 mL (10 mg/mL) solution in a single-dose vial. Patients are premedicated with an intravenous histamine-1 receptor antagonist (e.g., diphenhydramine hydrochloride) before each infusion; or, for patients who have experienced a Grade 1 or 2 IRR, premedicate with a histamine-1 receptor antagonist, dexamethasone (or equivalent), and acetaminophen prior to each infusion. For gastric cancer, 8 mg/kg is administered every 2 weeks as a single agent or in combination with weekly paclitaxel. For non-small cell lung cancer (NSCLC), 10 mg/kg is administered on Day 1 of a 21-day cycle prior to docetaxel. For colorectal cancer, 8 mg/kg is administered every 2 weeks prior to FOLFIRI. For hepatocellular carcinoma, 8 mg/kg is administered every 2 weeks. ATEs, proteinuria, and hypertension are among the adverse events that may be induced by ramucirumab administration. For the first occurrence of increased urine protein levels greater than or equal to 2 g per 24 hours, doctors may withhold ramucirumab until urine protein level is less than 2 g per 24 hours and resume at a reduced dose (reduce 8 mg dose to 6 mg, and 10

mg dose to 8 mg). Upon a recurrence of urine protein level greater than 2 g per 24 hours following initial dose reduction, doctors may withhold ramucirumab until urine protein level is less than 2 g per 24 hours and resume at a reduced dose (reduce 6 mg dose to 5 mg, and 8 mg dose to 6 mg). Ramucirumab is permanently discontinued for urine protein levels greater than 3 g per 24 hours or nephrotic syndrome. For hypertensive adverse events, blood pressure should be monitored and hypertension should be treated. Ramucirumab should be withheld for severe hypertension until it is controlled; and should be permanently discontinued if it cannot be controlled with antihypertensive therapy and for hypertensive crisis or hypertensive encephalopathy

[0085] In embodiments, the VEGF-pathway inhibitor is cabozantinib. Cabozantinib (CABOMETRYX, COMETRIQ) is a kinase inhibitor. CABOMETRYX is indicated for the treatment of advanced renal cell carcinoma (RCC) and patients with hepatocellular carcinoma (HCC) who have been previously treated with sorafenib CABOMETRYX is provided as 20 mg, 40 mg, and 60 mg tablets and is administered once daily at a dose of 60 mg orally. COMETRIQ® is indicated for the treatment of patients with progressive, metastatic medullary thyroid cancer (MTC). The recommended dose is 140 mg orally, once daily, and COMETRIQ is supplied as a 20 mg or 80 mg capsule.

[0086] For both CABOMETRYX and COMETRIZ, doses can be reduced if coadministered with strong CYP3A4 inhibitors (e.g., ketoconazole, ritonavir, clarithromycin), or if adverse reactions occur. For example, CABOMETRYX can be reduced from 60 mg daily to 40 mg daily, or from 40 mg daily to 20 mg daily, and if 20 mg daily is not tolerated, CABOMETRYX should be discontinued; and COMETRIZ daily administration can be reduced by 40 mg (e.g., from 140 to 100, or from 100 to 60). For coadministration with strong CYP3A4 inducers, CABOMETRYX should be increased by 20 mg daily (for example, from 60 mg to 80 mg daily or from 40 mg to 60 mg daily) as tolerated; and COMETRIQ should be increased by 40 mg (e.g., 140 mg to 180 mg daily or 100 mg to 140 mg daily) as tolerated. Patients are monitored for hypertension and proteinuria, and cabozantinib is interrupted for hypertension that is not adequately controlled with anti-hypertensive therapy; and is discontinued for hypertensive crisis or severe hypertension that cannot be controlled with anti-hypertensive therapy. Cabozantinib is discontinued for nephrotic syndrome.

[0087] In embodiments, the VEGF-pathway inhibitor is pazopanib. Pazopanib (VOTRIENT) is a kinase inhibitor indicated for the treatment of patients with advanced renal cell carcinoma (RCC) or advanced soft tissue sarcoma (STS) who have received prior chemotherapy. 800 mg is administered once daily. For RCC, the initial dose reduction should be 400 mg, and

additional dose decrease or increase should be in 200-mg steps based on individual tolerability. For STS, a decrease or increase should be in 200-mg steps based on individual tolerability. The recommended dose for patients with moderate hepatic impairment is 200 mg orally once daily and pazopanib is not recommended in patients with severe hepatic impairment. Concomitant use with strong CYP3A4 inhibitors should be avoided; if it is warranted, the pazopanib dose should be reduced to 400 mg. VOTRIENT is provided in a dosage form of 200 mg tablets. Cardiac dysfunction, arterial thromboembolic events, venous thromboembolic events, hypertension including hypertensive crisis, and proteinuria are among the adverse events for which patients should be monitored. Blood pressure should be well controlled before initiating pazopanib.

[0088] In embodiments, the VEGF-pathway inhibitor is sunitinib. Sunitinib malate (SUTENT) is a kinase inhibitor indicated for treatment of gastrointestinal stromal tumor (GIST) after disease progression on or intolerance to imatinib mesylate, treatment of advanced RCC, adjuvant treatment of adult patients at high risk of recurrent ACC following nephrectomy, and treatment of progressive, well-differentiated pancreatic neuroendocrine tumors (pNET) in patients with unresectable locally advanced or metastatic disease. The dosage form of sunitinib malate is 12.5 mg, 25 mg, 37.5 mg, or 50 mg capsules. For GIST and advanced RCC, the treatment regimen is 50 mg orally once daily, 4 weeks on treatment followed by 2 weeks off. For adjuvant RCC, the treatment regimen is 50 mg orally once daily, 4 weeks on treatment followed by 2 weeks off for nine 6-week cycles. For pNET, the treatment regimen is 37.5 mg orally once daily, continuously without a scheduled off-treatment period. Strong CYP3A4 inhibitors such as ketoconazole may increase sunitinib plasma concentrations and coadministration should be avoided. A dose reduction for to a minimum of 37.5 mg (GIST and RCC) or 25 mg (pNET) daily should be considered if sunitinib must be co-administered with a strong CYP3A4 inhibitor. CYP3A4 inducers such as rifampin may decrease sunitinib plasma concentrations and coadministration should be avoided. A dose increase for to a maximum of 87.5 mg (GIST and RCC) or 62.5 mg (pNET) daily should be considered if sunitinib must be co-administered with a CYP3A4 inducer. Adverse events that may occur and should be monitored for include cardiovascular events, hypertension, and proteinuria.

[0089] In embodiments, the VEGF-pathway inhibitor is regorafenib. Regorafenib (STIVARGA) is a kinase inhibitor indicated for the treatment of patients with metastatic colorectal cancer (CRC) who have been previously treated with fluoropyrimidine-, oxaliplatin- and irinotecan-based chemotherapy, an antiVEGF therapy, and, if RAS wild-type, an anti-EGFR therapy; patients with locally advanced, unresectable or metastatic GIST who have been

previously treated with imatinib mesylate and sunitinib malate; and HCC patients who have been previously treated with sorafenib. The dosage form is 40 mg tablets. The recommended dose is 160 mg orally, once daily for the first 21 days of each 28-day cycle. If dose modifications are required, the dose should be reduced in 40 mg (one tablet) increments; the lowest recommended daily dose of regorafenib is 80 mg daily. Regorafenib should be temporarily or permanently withheld for severe or uncontrolled hypertension. For cardiac ischemia and infarction, regorafenib should be withheld and resumed only after resolution of acute ischemic events.

[0090] In embodiments, the VEGF-pathway inhibitor is axitinib. Axitinib (INLYTA) is a kinase inhibitor indicated for the treatment of advanced RCC after failure of one prior systemic therapy. Axitinib is provided in a dosage form 1 mg and 5 mg tablets. The starting dose is 5 mg orally twice daily. Over the course of treatment, patients who tolerate axitinib for at least two consecutive weeks with no adverse reactions >Grade 2 (according to the CTCAE), are normotensive, and are not receiving anti-hypertension medication, may have their dose increased. When a dose increase from 5 mg twice daily is recommended, the axitinib dose may be increased to 7 mg twice daily, and further to 10 mg twice daily using the same criteria. Over the course of treatment, management of some adverse drug reactions may require temporary interruption or permanent discontinuation and/or dose reduction. If dose reduction from 5 mg twice daily is required, the recommended dose is 3 mg twice daily. If additional dose reduction is required, the recommended dose is 2 mg twice daily. If coadministration with strong CYP4/5 inhibitors is required, the dose of axitinib should be decreased by approximately half. Blood pressure should be well-controlled prior to initiating axitinib therapy and patients should be monitored for hypertension and treated as needed. For persistent hypertension despite use of anti-hypertensive medications, the axitinib dose should be reduced. Patients should also be monitored for arterial and venous thromboembolic events, cardiac failure, and proteinuria. For moderate to severe proteinuria, the axitinib dose should be reduced or temporarily interrupted

[0091] In embodiments, the VEGF-pathway inhibitor is LONSURF. LONSURF is a combination of trifluridine, a nucleoside metabolic inhibitor, and tipiracil, a thymidine phosphorylase inhibitor, and is indicated for the treatment of adult patients with metastatic colorectal cancer who have been previously treated with fluoropyrimidine-, oxaliplatin- and irinotecan-based chemotherapy, an anti-VEGF biological therapy, and if RAS wild-type, an anti-EGFR therapy; or for the treatment of metastatic gastric or gastroesophageal junction adenocarcinoma previously treated with at least two prior lines of chemotherapy that included

a fluoropyrimidine, a platinum, either a taxane or irinotecan, and if appropriate, HER2/neu-targeted therapy. The dosage form of LONSURF® is 15 mg trifluridine/6.14 mg tipiracil or 20 mg trifluridine/8.19 mg tipiracil. The recommended dosage is 35 mg/m² up to a maximum of 80 mg per dose (based on the trifluridine component) orally twice daily with food on Days 1 through 5 and Days 8 through 12 of each 28-day cycle. Doses are rounded to the nearest 5 mg increment. Within a treatment cycle, LONSURF is withheld for any of the following: absolute neutrophil count (ANC) less than 500/mm³ or febrile neutropenia, platelets less than 50,000/mm³, Grade 3 or 4 non-hematologic adverse reaction. After recovery, LONSURF can be resumed after reducing the dose by 5 mg/m²/dose. A maximum of 3 dose reductions are permitted. LONSURF dosage is not escalated after it has been reduced. LONSURF is discontinued in patients who are unable to tolerate a dose of 20 mg/m² orally twice daily.

[0092] In embodiments, the VEGF-pathway inhibitor is ponatinib. Ponatinib (ICLUSIG) is a kinase inhibitor indicated for treatment of adult patients with chronic phase, accelerated phase, or blast phase chronic myeloid leukemia (CML) or Ph+ ALL for whom no other tyrosine kinase inhibitor (TKI) therapy is indicated; or for treatment of adult patients with T315I-positive CML (chronic phase, accelerated phase, or blast phase) or T315I-positive Philadelphia chromosome positive acute lymphoblastic leukemia (Ph+ ALL). The dosage form is 15 mg, 30 mg, and 45 mg tablets. The recommended starting dose is 45 mg taken orally once daily with or without food. Dose modifications may be made for neutropenia and thrombocytopenia that are unrelated to leukemia; or for hepatotoxicity or pancreatitis and elevation of lipase. The recommended dose is reduced to 30 mg once daily when administering ICLUSIG with strong CYP3A inhibitors. Arterial occlusion, venous thromboembolism, heart failure, hypertension, and cardiac arrhythmias are among the adverse events that can occur. Blood pressure should be monitored.

[0093] In embodiments, the VEGF-pathway inhibitor is vandetanib. Vandetanib (CAPRELSA) is a kinase inhibitor indicated for the treatment of symptomatic or progressive medullary thyroid cancer in patients with unresectable locally advanced or metastatic disease. The dosage form is 100 mg and 300 mg tablets, and the dosing regimen is 300 mg once daily. The dose can be reduced to 200 mg (two 100 mg tablets) and then to 100 mg for CTCAE Grade 3 or greater toxicities. Vandetanib should be discontinued or interrupted in the event of ischemic cerebrovascular events, hemorrhage, heart failure, diarrhea, hypertension, and/or reversible posterior leukoencephalopathy syndrome.

[0094] In embodiments, the VEGF-pathway inhibitor is sorafenib. Sorafenib (NEXAVAR) is a kinase inhibitor indicated for the treatment of unresectable HCC, advanced RCC, and locally

recurrent or metastatic, progressive, differentiated thyroid carcinoma refractory to radioactive iodine treatment. The dosage form is 200 mg tablets. For dosing, 400 mg is administered orally twice daily at least 1 hour before or 2 hours after a meal. Treatment should continue until the patient is no longer clinically benefiting from therapy or until unacceptable toxicity occurs. When dose reduction is necessary, the dose may be reduced to 400 mg once daily. If additional dose reduction is required, vandetanib may be reduced to a single 400 mg dose every other day. Dermatologic toxicities, cardiovascular events, and hypertension should be monitored.

[0095] In embodiments, the VEGF-pathway inhibitor is everolimus. Everolimus is an inhibitor of mammalian target of rapamycin (mTOR) marketed as AFINITOR, AFINITOR DISPERZ, or ZORTRESS. AFINITOR is indicated for treatment of postmenopausal women with advanced hormone receptor-positive, HER2-negative breast cancer in combination with exemestane after failure of treatment with letrozole or anastrozole; adults with progressive neuroendocrine tumors of pancreatic origin (PNET) and adults with progressive, well-differentiated, non-functional neuroendocrine tumors (NET) of gastrointestinal (GI) or lung origin that are unresectable, locally advanced or metastatic; adults with advanced RCC after failure of treatment with sunitinib or sorafenib; and adults with renal angiomyolipoma and tuberous sclerosis complex (TSC), not requiring immediate surgery. AFINITOR and AFINITOR DISPERZ are indicated for the treatment of adult and pediatric patients aged 1 year and older with TSC who have subependymal giant cell astrocytoma (SEGA) that requires therapeutic intervention but cannot be curatively resected. AFINITOR DISPERZ is also indicated for the adjunctive treatment of adult and pediatric patients aged 2 years and older with TSC associated partial-onset seizures. Zortess is indicated for prophylaxis of kidney transplant rejection (in combination with basiliximab, cyclosporine, and corticosteroids) or liver transplant rejection (in combination with tacrolimus and corticosteroids). The dosage form of AFINITOR is 2.5 mg, 5 mg, 7.5 mg, and 10 mg tablets; the dosage form of AFINITOR DISPERZ is 2 mg, 3mg, and 5 mg tablets; the dosage form of ZORTRESS is 0.25 mg, 0.5 mg, and 0.75 mg. For breast cancer, NET, RCC, and TSC-associated angiomyolipoma, the approved dosage is 10 mg orally once daily. For TSC-associated SEGA, the approved dosage is 4.5 mg/m² orally once daily, with dose adjustments to attain trough concentrations of 5-15 mg/mL. For kidney transplantation, the starting dose is 0.75 mg orally twice daily starting as soon as possible after transplantation; for liver transplantation the starting dose is 1.0 mg twice daily starting 30 days after transplantation. Everolimus concentrations are monitored and maintenance doses are adjusted to achieve trough concentrations within 3-8 ng/mL target range

using LC/MS/MS assay method. Patients taking concomitant angiotensin-converting enzyme (ACE) inhibitors may be at increased risk of angioedema and proteinuria.

[0096] In embodiments, the VEGF-pathway inhibitor is thalidomide. Thalidomide (THALOMID) is indicated for the treatment of patients with newly diagnosed multiple myeloma (MM) in combination with dexamethasone; treatment of acute treatment of the cutaneous manifestations of moderate to severe erythema nodosum leprosum (ENL); and as a maintenance therapy for prevention and suppression of the cutaneous manifestations of ENL recurrence. Thalidomide is provided in a dosage form of 50 mg, 100 mg, 150 mg, and 200 mg. For MM, patients are administered 200 mg orally once daily, and the recommended dose of dexamethasone is 40 mg/day on days 1-4, 9-12, and 17-20 every 28 days. For ENL, patients are administered 100 to 300 mg/day for an episode of cutaneous ENL and up to 400 mg/day for severe cutaneous ENL. Dosing is continued until signs and symptoms of active reaction have subsided, usually a period of at least 2 weeks. Patients should be monitored for venous thromboembolism and ischemic heart disease (including myocardial infarction) and stroke.

[0097] In embodiments, the VEGF-pathway inhibitor is temsirolimus. Temsirolimus (TORISEL) is a kinase inhibitor indicated for treatment of advanced RCC. The dosage form is a 25 mg/mL solution for injection. The recommended dose of TORISEL is 25 mg infused over a 30-60 minute period once a week, until disease progression or unacceptable toxicity. Antihistamine pre-treatment is recommended. Temsirolimus should be held for absolute neutrophil count (ANC) $<1,000/\text{mm}^3$, platelet count $<75,000/\text{mm}^3$, or NCI CTCAE grade 3 or greater adverse reactions. Once toxicities have resolved to grade 2 or less, it may be restarted with the dose reduced by 5 mg/week to a dose no lower than 15 mg/week. The concomitant use of strong CYP3A4 inhibitors should be avoided (e.g. ketoconazole, itraconazole, clarithromycin, atazanavir, indinavir, nefazodone, nelfinavir, ritonavir, saquinavir, telithromycin, and voriconazole). Grapefruit juice may also increase plasma concentrations of sirolimus (a major metabolite of temsirolimus) and should be avoided. If patients must be co-administered a strong CYP3A4 inhibitor, based on pharmacokinetic studies, a temsirolimus dose reduction to 12.5 mg/week should be considered. The use of concomitant strong CYP3A4 inducers should be avoided (e.g. dexamethasone, phenytoin, carbamazepine, rifampin, rifabutin, rifampacin, phenobarbital). If patients must be co-administered a strong CYP3A4 inducer, based on pharmacokinetic studies, a temsirolimus dose increase from 25 mg/week up to 50 mg/week should be considered. Patients should be monitored for proteinuria and nephrotic syndrome.

[0098] In embodiments, the VEGF-pathway inhibitor is interferon alfa. Interferon alfa (interferon alfa-2B, interferon alfa-N3, peginterferon alfa-2B, and peginterferon alfa-2A) is marketed as INTRON A, PEGASYS, PEGINTRON, ALFERON N, and SYLATRON. INTRON A is indicated for treatment with hairy cell leukemia (2 million IU/m² administered intramuscularly or subcutaneously 3 times per week for up to 6 months), malignant melanoma (20 million IU/m² as an intravenous infusion 5 consecutive days per week, for 4 weeks, with maintenance of treatment of 10 million IU/m² as a subcutaneous injection three times per week for 48 weeks), follicular lymphoma (5 million IU subcutaneously three times per week for up to 18 months in conjunction with anthracycline-containing chemotherapy regimen and following completion of the chemotherapy regimen), condylomata acuminata 1.0 million IU per lesion in a maximum of 5 lesions in a single course; lesions are injected three times weekly on alternate days for 3 weeks), AIDS-related Kaposi's sarcoma (30 million IU/m²/dose administered subcutaneously or intramuscularly three times per week until disease progression or maximal response has been achieved after 16 weeks of treatment), chronic hepatitis C (3 million IU three times per week subcutaneously or intramuscularly), and chronic hepatitis B (in adults, 30 to 35 million IU per week, administered subcutaneously or intramuscularly, either as 5 million IU daily or as 10 million IU three times per week for 16 weeks; and in pediatrics, 3 million IU/m² three times per week for the first week followed by dose escalation to 6 million IU/m² three times per week subcutaneously, for a total duration of 16 to 24 weeks). PEGASYS is indicated for chronic hepatitis (180 mcg per week or 1.5 mcg/kg/week in adults; and 180 mcg/1.73 m²xBSA per week or 60 mcg/m² per week in pediatrics). Potential adverse events include cardiovascular disorders and ischemic and hemorrhagic cerebrovascular events.

[0099] In embodiments, the VEGF-pathway inhibitor is rhEndostatin. rhEndostatin (ENDOSTAR) is indicated for HCC, NSCLC (squamous or non-squamous), postoperative NSCLC, advanced NSCLC with EGFR mutations, solid tumors in pediatric patients, and metastatic melanoma. For HCC, dosing is 30mg/d, from 5 days before radiotherapy, for 7 days, 21 per cycle, with concurrent standard radiotherapy for HCC. For squamous NSCLC, dosing is 15mg/m² for 5 days and 200 mg of pembrolizumab at day 1 in each cycle, repeating every 3 weeks till PD or unacceptable toxicities. Squamous NSCLC patients also receive carboplatin (5U/AUC) or cisplatin (75 mg/m²) and [nab]-paclitaxel (100 mg/m²) for the first 4 cycles. For non-squamous NSCLC, dosing is 15 mg/m² for 5 days, 200 mg of pembrolizumab at day 1 and pemetrexed (500 mg/m² day 1) are given in each cycle, repeating every 3 weeks till to PD or unacceptable toxicities. Squamous and non-squamous NSCLC also receive carboplatin (5U/AUC) or cisplatin (75 mg/m²) and [nab]-paclitaxel (100 mg/m²) (squamous) or

pemetrexed (500 mg/m² day 1) (non-squamous) for the first 4 cycles. For untreated stage IIIB/IV NSCLC, dosing is continuous intravenous infusion rh-endostatin at 7.5 mg/m² for 14 days each cycle, 21 days as one cycle, 4 cycles in total, with docetaxel or pemetrexed. For advanced NSCLC with EGFR mutations, dosing is 15 mg CIV days 1-9, Q3W with icotinib. For postoperative NSCLC, dosing is rh-Endostatin 7.5 mg/m² days 1-14; 21 d as a cycle with pemetrexed and cis-platinum or with docetaxel and cis-platinum. For phase III B/IV squamous lung cancer with GP, dosing is rh-Endostatin at 7.5 mg/m², continuous intravenous infusion for 14 days each cycle, 21 days as one cycle, 4 cycles in total with gemcitabine, cisplatin. For advanced NSCLC with docetaxel, dosing is rh-endostatin at 7.5 mg/m², IV on day 1-14 of each 21-28 day cycle with docetaxel. For metastatic melanoma, dosing is based on body surface area as 15 mg/m² rh-endostatin with cisplatin and dacarbazine.

[0100] In embodiments, the VEGF-pathway inhibitor is cediranib. Cediranib (RECENTIN) is approved for use in cancer, including ovarian, breast, colorectal, metastatic colorectal, renal, lung, non-small cell lung cancer, sarcoma, glioblastoma, fallopian tube, peritoneal cancer, and triple-negative breast cancer. Dosing is as follows. For metastatic colorectal cancer: 20 mg cediranib once a day in combination with FOLFOX or XELOX chemotherapy. For recurrent glioblastoma: 30 mg as monotherapy once daily; 20 mg once daily in combination with lomustine (110 mg/m²) every 6 weeks. For recurrent, platinum chemotherapy-sensitive disease or ovarian cancer related to mutations in BRCA genes: 30 mg once a day with 200 mg olaparib twice a day. For recurrent ovarian, fallopian tube, peritoneal, or triple-negative breast cancer: (1) 20 mg daily and olaparib 100 mg twice daily (BID) (2) cediranib 20 mg daily, olaparib 200mg BID; (3) cediranib 30mg daily, olaparib 200mg BID; (4) cediranib 30mg daily, olaparib 400mg BID. For advanced non-small cell lung cancer: cisplatin 80 mg/m² on day 1 and gemcitabine 1250 mg/m² on days 1 and 8 of a 3-week cycle, and daily oral cediranib at either 30 mg or 45 mg.

[0101] In embodiments, the VEGF-pathway inhibitor is semaxanib. Semaxanib is a tyrosine kinase inhibitor indicated for colorectal cancer, solid tumors, brain tumors, kidney cancer, melanoma, head and neck cancer, hematologic cancers, mesothelioma, soft tissue sarcomas, breast cancer, AIDS-Related Kaposi's Sarcoma, multiple myeloma, cervical cancer, prostate cancer, and ovarian cancer. For metastatic melanoma, 145 mg/m² semaxanib is administered intravenously twice-weekly in combination with thalidomide, commencing at 200 mg daily with inpatient dose escalation as tolerated; or 85 or 145 mg/m² in combination with standard irinotecan/bolus 5-fluorouracil/leucovorin (IFL) for 4 weeks on/2 weeks off. For solid tumors, semaxanib is administered at a dose of 145 mg/m² twice weekly. For metastatic colon cancer,

semaxanib is administered at a dose of 85 or 145 mg/m² twice weekly in combination with fluorouracil and leucovorin (given either weekly or daily for 5 days every 4 weeks). For Kaposi's sarcoma, semaxanib is administered at a dose of 65–145 mg/m² i.v. biw for six cycles (of 29 days).

[0102] In embodiments, the VEGF-pathway inhibitor is pomalidomide. Pomalidomide (POMALYST) is a thalidomide analogue indicated for the treatment of adult patients with multiple myeloma (MM) who have received at least two prior therapies including lenalidomide and a proteasome inhibitor and have demonstrated disease progression on or within 60 days of completion of the last therapy; in combination with dexamethasone. POMALYST is also indicated for adult patients with AIDS-related Kaposi sarcoma (KS) after failure of highly active antiretroviral therapy (HAART) or in patients with KS who are HIV negative. For MM, pomalidomide is administered at a dose of 4 mg per day orally on days 1 through 21 of repeated 28-day cycles in combination with dexamethasone until disease progression. For KS, pomalidomide is administered at a dose of 5 mg per day taken orally on Days 1 through 21 of repeated 28-day cycles until disease progression or unacceptable toxicity. Coadministration with strong CYP1A2 Inhibitors should be avoided, but if unavoidable, pomalidomide dosing should be reduced to 2 mg. The dosage form of pomalidomide is 1 mg, 2 mg, 3 mg, or 4 mg capsules. Deep venous thrombosis (DVT), pulmonary embolism (PE), myocardial infarction, and stroke may occur in patients with multiple myeloma treated with POMALYST.

[0103] In embodiments, the VEGF-pathway inhibitor is alitretinoin. Alitretinoin (PANRETIN) is a gel indicated for topical treatment of cutaneous lesions in patients with AIDS-related Kaposi's sarcoma. Panretin gel is not indicated when systemic anti-KS therapy is required (e.g., more than 10 new KS lesions in the prior month, symptomatic lymphedema, symptomatic pulmonary KS, or symptomatic visceral involvement). Panretin gel should initially be applied two (2) times a day to cutaneous KS lesions. The application frequency can be gradually increased to three (3) or four (4) times a day according to individual lesion tolerance. Panretin gel is available in tubes containing 60 grams.

[0104] In embodiments, the VEGF-pathway inhibitor is imiquimod. Imiquimod is marketed as ALDARA and ZYCLARA. ALDARA is a 5% cream supplied in single-use packets (24 per box), each of which contains 250 mg of the cream, equivalent to 12.5 mg of imiquimod. ZYCLARA is provided as a 2.5% or 3.75% cream in packets or a pump. Imiquimod is indicated for the topical treatment of clinically typical, nonhyperkeratotic, nonhypertrophic actinic keratoses (AK) on the face or scalp in immunocompetent adults; biopsy-confirmed, primary superficial basal cell carcinoma (sBCC) in immunocompetent adults; maximum tumor

diameter of 2.0 cm on trunk, neck, or extremities (excluding hands and feet), only when surgical methods are medically less appropriate and patient follow-up can be reasonably assured; and external genital and perianal warts/condyloma acuminata in patients 12 years old or older.

[0105] In embodiments, the VEGF-pathway inhibitor is sinecatechins. Sinecatechins (VEREGEN) is a 15% topical ointment indicated for the treatment of external genital and perianal warts (Condylomata acuminata) in immunocompetent patients 18 years and older. VEREGEN is to be applied three times per day to all external genital and perianal warts.

[0106] In embodiments, the VEGF-pathway inhibitor is vismodegib. Vismodegib (ERIVEDGE) is a hedgehog pathway inhibitor indicated for the treatment of adults with metastatic basal cell carcinoma, or with locally advanced basal cell carcinoma that has recurred following surgery or who are not candidates for surgery and who are not candidates for radiation. The recommended dosage is 150 mg orally once daily. The dosage form is 150 mg capsules.

[0107] In embodiments, the VEGF-pathway inhibitor is sonidegib. Sonidegib (ODOMZO) is a hedgehog pathway inhibitor indicated for the treatment of adult patients with locally advanced basal cell carcinoma (BCC) that has recurred following surgery or radiation therapy, or those who are not candidates for surgery or radiation therapy. The recommended dosage is 200 mg orally once daily taken on an empty stomach, at least 1 hour before or 2 hours after a meal. Serum creatine kinase (CK) levels and renal function tests are prior to initiating ODOMZO treatment. The dosage form is 200 mg capsules.

[0108] In embodiments, the VEGF-pathway inhibitor is pegaptanib sodium. Pegaptanib sodium (MACUGEN) is indicated for the treatment of neovascular (wet) age-related macular degeneration. MACUGEN is administered in a dose of 0.3 mg once every six weeks by intravitreal injection into the eye. The dosage form is a 0.3 mg/90 µL solution in a single-use syringe for intravitreal injection.

[0109] In embodiments, the VEGF-pathway inhibitor is dexamethasone. Dexamethasone intravitreal implant (OZURDEX) is a corticosteroid indicated for the treatment of macular edema following branch retinal vein occlusion (BRVO) or central retinal vein occlusion (CRVO), the treatment of non-infectious uveitis affecting the posterior segment of the eye, or the treatment of diabetic macular edema. The dosage form is an intravitreal implant containing 0.7 mg dexamethasone in the NOVADUR solid polymer drug delivery system.

[0110] In embodiments, the VEGF-pathway inhibitor is fluocinolone acetonide. Fluocinolone acetonide (ILUVIEN) contains a corticosteroid and is indicated for the treatment of diabetic

macular edema (DME) in patients who have been previously treated with a course of corticosteroids and did not have a clinically significant rise in intraocular pressure. The dosage form is a non-bioerodable intravitreal implant containing 0.19 mg fluocinolone acetonide in a drug delivery system, and is intended for intravitreal injection.

[0111] In embodiments, the VEGF-pathway inhibitor is conbercept. Conbercept (COMPAQ SIQQ) is indicated for treatment of age-related macular degeneration (AMD) and other macular diseases, Idiopathic Choroidal Neovascularization, Diabetic Retinopathy, Macular Edema, Central Retinal Vein Occlusion, Tractional Retinal Detachment, Circumscribed Choroidal Haemangioma, uveitis, Polypoidal Choroidal Vasculopathy, and Corneal Neovascularization. For AMD and other retinal vascular disorders, conbercept may be administered at a dose of 0.5 mg/eye monthly for 3 months followed by 0.5 mg/eye every 3 months; or just 0.5 mg/eye every 3 months without the 3 month loading period; or 0.5 mg or 2.0 mg for 3 consecutive monthly doses, after which either monthly or as-needed (PRN) therapy is administered at the same previous dose; or 0.5 mg every 8 weeks and 1.0 mg every 12 weeks after 3 monthly injections as a loading phase.

[0112] In embodiments, the VEGF-pathway inhibitor is brolucizumab. Brolucizumab-dbl (BEOVU) is a human vascular endothelial growth factor (VEGF) inhibitor indicated for the treatment of AMD. BEOVU is administered by intravitreal injection. The recommended dose for BEOVU is 6 mg (0.05 mL of 120 mg/mL solution) monthly (approximately every 25-31 days) for the first three doses, followed by one dose of 6 mg (0.05 mL) every 8-12 weeks. The dosage form is a 6 mg/0.05 mL solution for intravitreal injection in a single-dose vial. There is a potential risk of arterial thromboembolic events (ATE) following intravitreal use of VEGF inhibitors

[0113] In embodiments, the VEGF-pathway inhibitor is selpercatinib. Selpercatinib (RETEVMO) is a kinase inhibitor indicated for the treatment of adult patients with metastatic RET fusion-positive NSCLC, adult and pediatric patients 12 years of age and older with advanced or metastatic RET-mutant medullary thyroid cancer (MTC) who require systemic therapy, and adult and pediatric patients 12 years of age and older with advanced or metastatic RET fusion-positive thyroid cancer who require systemic therapy and who are radioactive iodine-refractory (if radioactive iodine is appropriate). Patients are selected for treatment with RETEVMO based on the presence of a RET gene fusion (NSCLC or thyroid) or specific RET gene mutation (MTC). The recommended dosage in adults and pediatric patients 12 years of age or older is based on weight as follows. Less than 50 kg: 120 mg orally twice daily; 50 kg or greater: 160 mg orally twice daily. RETEVMO may be administered orally twice daily

(approximately every 12 hours) until disease progression or unacceptable toxicity. Concomitant use of strong and moderate CYP3A inhibitors should be avoided, but if it cannot be avoided, the RETEVMO dose may be reduced as follows. If taking 120 mg twice daily: reduce to 80 mg twice daily with a moderate inhibitor and 40 mg twice daily with a strong inhibitor; if taking 160 mg twice daily: reduce to 120 mg twice daily with a moderate inhibitor and 80 mg twice daily with a strong inhibitor. Concomitant use of a PPI, a histamine-2 (H2) receptor antagonist, or a locally-acting antacid with RETEVMO should be avoided, but if it cannot be avoided, RETEVMO may be administered with food and/or 2 hours before or 10 hours after an H2 receptor antagonist; or 2 hours before or 2 hours after a locally-acting antacid. Dosing may also be reduced for severe hepatic impairment. The dosage form is 40 mg and 80 mg capsules. RETEVMO should not be initiated in patients with uncontrolled hypertension. Blood pressure should be monitored and RETEVMO should be withheld, reduced in dose, or permanently halted based on severity.

[0114] In embodiments, the VEGF-pathway inhibitor is nintedanib (OFEV). Nintedanib is a kinase inhibitor indicated for treatment of idiopathic pulmonary fibrosis (IPF), treatment of chronic fibrosing interstitial lung diseases (ILDs) with a progressive phenotype, and for slowing the rate of decline in pulmonary function in patients with systemic sclerosis-associated interstitial lung disease. Nintedanib is administered at a dose of 150 mg twice daily, about 12 hours apart. The dosage form is 150 mg or 100 mg capsules. Arterial thromboembolic events have been reported. Caution should be taken when treating patients at higher cardiovascular risk including known coronary artery disease. Treatment may be interrupted in patients who develop signs or symptoms of acute myocardial ischemia. For patients with mild hepatic impairment, the dose may be modified to 100 mg twice daily approximately 12 hours apart. In addition to symptomatic treatment, if applicable, dose reduction or temporary interruption may be indicated for the management of adverse reactions, until the specific adverse reaction resolves to levels that allow continuation of therapy. Treatment may be resumed at the full dosage (150 mg twice daily), or at the reduced dosage (100 mg twice daily), which subsequently may be increased to the full dosage. If a patient does not tolerate 100 mg twice daily, treatment with nintedanib may be discontinued. Dose modifications or interruptions may be necessary for liver enzyme elevations. Liver function tests (aspartate aminotransferase (AST), alanine aminotransferase (ALT), and bilirubin) may be conducted prior to initiation of treatment with nintedanib, at regular intervals during the first three months of treatment, and periodically thereafter or as clinically indicated. In patients who report symptoms that may indicate liver injury, including fatigue, anorexia, right upper abdominal discomfort, dark urine

or jaundice, liver tests may be measured promptly. In patients with AST or ALT greater than 3 times the upper limit of normal (ULN) with signs or symptoms of liver injury and for AST or ALT elevations greater than 5 times the upper limit of normal, treatment may be discontinued. For AST or ALT greater than 3 times to less than 5 times the ULN without signs of liver damage, treatment may be interrupted or reduced to 100 mg twice daily. Once liver enzymes have returned to baseline values, treatment may be reintroduced at a reduced dosage (100 mg twice daily), which subsequently may be increased to the full dosage (150 mg twice daily).

[0115] In embodiments, the VEGF-pathway inhibitor is apatinib. Apatinib is indicated for treatment of advanced or metastatic gastric carcinoma, metastatic breast cancer, advanced hepatocellular carcinoma, metastatic colorectal cancer, esophageal cancer (advanced esophageal squamous cell carcinoma), and glioblastoma. Apatinib generally may be administered at a dose of 750 mg once daily. Other possible doses include 250, 500, 750, 850, and 1000 mg once daily. For advanced or metastatic gastric carcinoma, apatinib may be administered at a dose of 850 mg once daily or 425 mg twice daily. For advanced progressed lung adenocarcinoma patients with EGFR-TKI resistance, apatinib may be administered at a dose of 500 mg/m² per day for 21 consecutive days alone or in combination with traditional chemotherapy drugs pemetrexed (50 mg/m², once every 21 days) and docetaxel (75 mg/m², once every 21 days). For metastatic colorectal cancer, apatinib may be administered at a dose of 125 mg, 250 mg, 500 mg, 850 mg once per day, alone or in combination with other agents in either 21 or 28 day cycles. For advanced esophageal squamous cell carcinoma, apatinib may be administered at a dose of 500 mg daily in a 28 day cycle, which may be reduced to 250 mg.

[0116] In embodiments, the VEGF-pathway inhibitor is motesanib. Motesanib is indicated for thyroid cancer (progressive or symptomatic, advanced or metastatic medullary thyroid cancer; progressive differentiated thyroid cancer), non-small cell lung cancer (advanced nonsquamous), gastrointestinal stromal cancer, colorectal cancer, breast cancer (HER2-negative locally recurrent or metastatic breast cancer), persistent or recurrent ovarian cancer, fallopian tube and primary peritoneal carcinomas, advanced solid tumors, and low-grade neuroendocrine tumors. For advanced nonsquamous non-small-cell lung cancer (NSCLC), motesanib may be administered at a dose of 125 mg once daily, or 75 mg twice daily (5 days on/2days off), both with carboplatin (AUC, 6 mg/ml min) and paclitaxel (200 mg/m²) for up to six 3-week cycles. For HER2-negative locally recurrent or metastatic breast cancer: motesanib 125 mg orally once per day with paclitaxel (90 mg/m² on days 1, 8, and 15 every 3 weeks). For progressive or symptomatic, advanced or metastatic medullary thyroid cancer, progressive differentiated thyroid cancer, advanced solid tumors, and for persistent or recurrent

ovarian, fallopian tube, and primary peritoneal carcinomas, motesanib may be administered at a dose of 125 mg daily. For low-grade neuroendocrine tumors, motesanib may be administered at a dose of 125 mg once daily in combination with octreotide-LAR (30 mg administered on day 1 of each cycle 28-day cycle).

[0117] VEGF-pathway inhibitors may be administered in combination with one or more additional anti-cancer therapies. For example, VEGF-pathway inhibitors may be administered in combination with surgical therapy, radiation therapy, chemotherapy, immunotherapies (e.g. checkpoint inhibitors, adoptive cell transfer, antibodies, vaccines, cytokines, etc.), targeted therapies (e.g. small-molecule drugs, antibodies), hormone therapy, stem-cell transplant, and the like. The subject may be a candidate for or currently provided with any suitable combination of therapies prior to determination of risk of VEGF-inhibitor toxicities in the subject. Any suitable combination of therapies (e.g. VEGF-inhibitors, other anti-cancer therapies, supportive therapies, or any combination thereof) may be provided to the subject following determination of risk in the subject.

[0118] Any of the therapies described herein (e.g. VEGF-pathway inhibitors, supportive therapies, other anti-cancer therapies) may be provided by any suitable route. For example, the therapy may be provided orally. Alternatively, the therapy may be provided parenterally. Suitable doses and modes of administration may be determined based upon various factors, including the age, sex, weight, health of the subject, other medications being administered to the subject, and the like, using routine techniques known in the art.

[0119] By way of example and not of limitation, examples of the present disclosure will now be provided.

EXPERIMENTAL EXAMPLES

Example 1

[0120] The objective of the current study was to perform a GWAS of four randomized phase III clinical trials from the Cancer and Leukemia Group B (CALGB, now Alliance for Clinical Trials in Oncology, Alliance) to identify novel genes and genetic variants that showed a consistent risk of toxicity across the different studies.

Methods

Patients and randomized, phase III clinical trials

[0121] CALGB 80303 was conducted in advanced pancreatic cancer patients treated with gemcitabine and either 10 mg/kg bevacizumab or placebo. CALGB 40503 was conducted in

hormone receptor-positive advanced-stage breast cancer patients treated with letrozole and either 15 mg/kg bevacizumab or placebo. CALGB 90401 was conducted in metastatic castration-resistant prostate cancer patients treated with docetaxel/prednisone with either 15 mg/kg bevacizumab or placebo. CALGB 40502 was conducted in locally recurrent or metastatic breast cancer patients treated with either nab-paclitaxel, ixabepilone, or paclitaxel, all administered in combination with 10 mg/kg bevacizumab. Patient eligibility, characteristics, stratifications, treatments, and the methods to detect progression of disease have been previously described.

Toxicity

[0122] Proteinuria and hypertension were recorded according to Common Toxicity Criteria for Adverse Events (CTCAE) version 3.0 (Table 1), per protocol. The composite toxicity is defined as the occurrence of either proteinuria or hypertension or both. For CALGB 40502, data on proteinuria and composite toxicity were not available. Urine protein levels were measured on day 1 and every four weeks after starting treatment in CALGB 80303; on day 1 of the 1st cycle and up to 5 days before or on the day of treatment for subsequent cycles in CALGB 40503; and within 48 hours prior to every treatment cycle in CALGB 90401. Blood pressure was obtained on day 1 of each cycle in all trials, and plus on day 15 in CALGB 80303.

Table 1. Hypertension and proteinuria grades of toxicity according to Common Toxicity Criteria of Adverse Events (CTCAE) v3.0.

Urine dipstick test result: 1+ (15-30 mg/dL), 2+ (100-300 mg/dL), 3+ (300-1000 mg/dL), and 4+ (>1000 mg/dL). *WNL* within normal limits.

Toxicity	Grade 1	Grade 2	Grade 3	Grade 4	Grade 5
Proteinuria	1+ or 0.15 – 1.0 g/24 hrs	2+ to 3+ or >1.0 – 3.5 g/24 hrs	4+ or >3.5 g/24 hrs	Nephrotic syndrome	Death
Hypertension	Asymptomatic, transient (<24 hrs) increase by >20 mmHg (diastolic) or to >150/100 if previously WNL; intervention not indicated	Recurrent or persistent (≥24 hrs) or symptomatic increase by >20 mmHg (diastolic) or to >150/100 if previously WNL; monotherapy may be indicated	Requiring more than one drug or more intensive therapy than previously	Life- threatening consequences (e.g., hypertensive crisis)	Death

[0123] Bevacizumab-related toxicity was defined as the occurrence of toxicity (grade ≥ 2 or grade ≥ 3 of hypertension, proteinuria, or either proteinuria or hypertension – composite toxicity) after the start of treatment. Only toxicities with attribution of “possibly related” or higher were included. The occurrence of treatment-terminating events was used for censoring, as they determined the exit of the patients from the trial. Treatment-terminating events included death, disease progression, other toxicities defined per protocol, withdrawal of consent, loss to follow up, or unknown recorded events. The time to event was reconstructed manually for each patient in each study, as performed previously. The time to event was calculated as the time from the first administration of bevacizumab to the first date of experiencing the toxicity of interest, or other treatment-terminating events, whichever occurred first.

Genotyping and quality control

[0124] DNA for genotyping was obtained from peripheral blood. The genotyping platforms used in each study are described in Table 2, and the number of SNPs used for analysis after quality control (QC) are described in FIG. 1. Additional information on the quality control procedures can be found in the individual publications of the GWAS data.

Table 2. Patients of European ancestry treated with bevacizumab used in the GWAS data.

CALGB Cancer and Leukemia Group B, *SD* standard deviation, composite toxicity is defined as the occurrence of either proteinuria or hypertension or both.

CALGB trial		80303 n=154	40503 n=105	90401 n=316	40502 n=466
Age	Mean (SD)	64.1 (10.2)	68.4 (8.3)	56.9 (11.7)	57.2 (10.7)
Gender	Male	90	0	316	0
	Female	64	105	0	466
Cancer type		Advanced pancreatic cancer	Hormone receptor-positive advanced-stage breast cancer	Metastatic castration-resistant prostate cancer	Recurrent or metastatic breast cancer
Treatment		Gemcitabine 1,000 mg/m ² on days 1, 8, and 15 plus either placebo or bevacizumab 10 mg/kg on days 1 and 15	Letrozole 2.5 mg orally/day plus either placebo or bevacizumab 15 mg/kg every 21 days	Docetaxel 75 mg/m ² in combination with prednisone 5 mg orally on day 1 plus either placebo or bevacizumab 15 mg/kg every 21 days	Paclitaxel 90 mg/m ² or nab-paclitaxel 150 mg/m ² or ixabepilone 16 mg/m ² on days 1, 8, and 15 plus bevacizumab 10 mg/kg on days 1 and 15
Genotype platform		Illumina HumanHap550-Quad	Illumina Human OmniExpressExome-8	Illumina HumanHap610-Quad	Illumina Human OmniExpressExome-8

	Grade $\geq$ 2	Grade $\geq$ 3	Grade $\geq$ 2	Grade $\geq$ 3	Grade $\geq$ 2	Grade $\geq$ 3	Grade $\geq$ 2	Grade $\geq$ 3
Hypertension (n, %)	26 (16.9)	19 (12.3)	53 (50.5)	29 (27.6)	47 (15.0)	22 (7.0)	143 (30.7)	50 (10.7)
Proteinuria (n, %)	26 (16.9)	9 (5.8)	32 (30.5)	10 (9.5)	20 (6.4)	5 (1.6)	-	-
Composite toxicity (n, %)	43 (27.9)	26 (16.9)	73 (69.5)	34 (32.4)	61 (19.4)	26 (8.2)	-	-

Statistical Analysis

SNP-based association testing

[0125] The association between SNPs and toxicities (grade $\geq$ 2 or grade $\geq$ 3) was tested in genetic European patients in the bevacizumab arm. Ethnicity information was determined by estimating the genetic ancestral origin of patients using the principal components analysis software implemented in Eigenstrat. A cause-specific Cox model, where the outcome is defined as the pair of time event and the censoring indicator, was fitted to obtain the estimate of the SNP effect (and the corresponding standard error estimate) on toxicity in each individual study. The analyses were powered against an additive genetic model. The inverse variance formula was used to combine the SNP effect in each study to obtain the estimate (β) of the SNP-toxicity association and its standard error. The heterogeneity across studies was examined by the Cochran's test (no heterogeneity was detected). Cox analyses for each variant, adjusting for age and gender, were performed by adding those variables as covariates in the model. The reported results are unadjusted, unless stated otherwise. The reported p values are not corrected for multiple comparisons. Quantile-quantile (Q-Q) plots were generated.

Gene-based association testing

[0126] Under the same model described above, a gene-based analysis was also performed. First, all the human protein-coding genes were mapped to SNPs according to the location of SNPs with a margin equaling 50 by using the R package "snplist". Next, the cause-specific Cox model was fitted to obtain the score statistics for SNP by toxicity association in each study. Last, the Sequence Kernel Association Test (SKAT) was used to combine the SNP-level test statistics. This method allowed for different directions of the SNP effect in a gene and could accommodate also common alleles. From the SKAT test, the weighted quadratic statistics were computed using the MASS software, with p-values determined by the re-sampling method. The reported results are unadjusted, unless stated otherwise. The reported p values are not corrected for multiple comparisons. Q-Q plots were also generated for this analysis.

Functional annotation of variants

[0127] Functional annotation of SNPs and genes was performed using the SCAN database. Variants were analyzed by the LDlink web-based application for analyses of linkage disequilibrium (LD). UCSC Genome Browser (<http://genome.ucsc.edu/>), RegulomeDB and

Haploreg v4 were used for functional inference. The Genotype-Tissue Expression project (GTEx v7) and NephQTL were used for expression quantitative trait loci (eQTL) analyses.

Results

[0128] A total of 1,041 cancer patients of European ancestry treated with bevacizumab with available genotyping information were included in the study. The characteristics of patients from each trial, as well as the prevalence of toxicities, are shown in **Table 2**. Grade ≥ 2 hypertension (15.0%-50.5%) was more prevalent than grade ≥ 2 proteinuria (5.4-30.5%). The prevalence of either grade ≥ 2 proteinuria or grade ≥ 2 hypertension (composite toxicity) was 19.4-69.5%. Considering only the patients who had both toxicities, the prevalence was 1.9%-11.4%. The prevalence of these toxicities was higher in female patients in the breast cancer studies (CALGB 40502 and 40503) than in male patients in the prostate cancer study (CALGB 90401). A higher prevalence was also observed in females compared to males in the pancreatic cancer study (CALGB 80303) (**Table 3**).

Table 3. Prevalence of hypertension and proteinuria in CALGB 80303 by gender.

Composite toxicity is defined as the occurrence of either proteinuria or hypertension or both.

	Grade ≥ 2		Grade 3	
	Female (n=64)	Male (n=90)	Female (n=64)	Male (n=90)
Hypertension (n, %)	14 (21.9)	12 (13.3)	9 (14.1)	10 (11.1)
Proteinuria (n, %)	11 (17.2)	15 (16.7)	6 (9.4)	3 (3.3)
Composite toxicity (n, %)	20 (31.2)	23 (25.6)	14 (21.9)	12 (13.3)

Variants and genes associated with bevacizumab-induced proteinuria

[0129] For the SNP-based analysis of grade ≥ 2 , the Manhattan and Q-Q plots are shown in **FIG. 2**. 90 variants were identified as associated with bevacizumab-induced proteinuria (**Table 4**).

Table 4. SNP's associated with Proteinuria (grade ≥2)

SNP	CH	BP	effect allele	reference allele	MAF 80303	MAF 40503	MAF 90401	gene	feature	Flanking gene	Flanking gene	p-value unadjusted	effect (β) unadjusted	p-value adjusted	effect (β) adjusted
rs339947	5	14071067	A	C	0.12	.	0.14	NA	NA	DNAH5	TRIO	7.66E-08	1.27	1.58E-07	1.26
rs13293961	9	104807170	A	C	.	.	0.08	CYLC2	missense	LOC100131879	SMC2	2.39E-06	1.56	2.60E-06	1.61
rs12612153	2	44755864	C	A	0.11	.	0.11	C2orf34	intron	PREPL	LOC100130502	3.89E-06	1.16	6.93E-06	1.15
rs7180310	15	22890430	A	C	0.06	0.05	.	NA	NA	SNORD116-24	SNORD116-25	4.10E-06	1.54	4.19E-06	1.55
rs12482855	21	42065030	A	G	0.06	0.06	0.06	NA	NA	RIPK4	PRDM15	6.28E-06	1.20	1.09E-05	1.20
rs408130	5	14059289	A	G	0.21	.	0.28	NA	NA	DNAH5	TRIO	6.33E-06	1.07	6.94E-06	1.09
rs418173	5	14058033	A	G	0.21	.	0.28	NA	NA	DNAH5	TRIO	6.33E-06	1.07	6.94E-06	1.09
rs11716628	3	35851495	G	A	.	0.18	.	NA	NA	ARPP-21	LOC100131711	6.87E-06	1.39	1.04E-05	1.39
rs7959783	12	67109382	G	A	0.31	0.26	0.33	NA	NA	MDM1	LOC729376	7.01E-06	0.72	6.56E-06	0.73
rs627761	11	125330918	G	A	0.10	.	0.09	LOC338667	intron	DDX25	CDON	7.49E-06	1.19	1.34E-05	1.18
rs2688994	3	126300783	A	G	0.13	0.14	0.14	SLC12A8	intron	HEG1	ZNF148	8.13E-06	0.92	4.38E-06	0.98
rs10486445	7	24980507	G	A	0.42	0.35	0.39	OSBP13	intron	DFNA5	CYCS	1.17E-05	0.75	1.11E-05	0.78
rs17345945	8	68674808	A	G	0.09	.	0.08	CPA6	intron	LOC100132812	PREX2	1.36E-05	1.15	1.30E-05	1.19
rs13276511	8	86959167	G	A	0.06	.	.	NA	NA	REXO117P	LOC642137	1.39E-05	1.40	4.01E-05	1.37

[illegible]

rs129	15	59578	C	T	.	0.42	.	NA	NA	RORA	VPS13C	3.60E-05	-1.32	6.94E-06	-1.33
10488		470								LOC4409	LOC7281				
rs761	3	85886	C	A	0.08	.	0.12	CADM2	intron	70	44	3.71E-05	1.04	3.43E-05	1.01
6936		475								LOC1001	HEY1	3.85E-05	1.16	3.15E-05	1.15
rs132	8	80730	G	A	.	0.23	.	STMN2	intron	28963					
55802		920									LOC4000	3.90E-05	0.91	2.09E-05	0.95
rs115	12	19614	A	G	0.50	.	0.49	NA	NA	AEBP2	13				
32247		829								LOC1001	HSP90AB	3.95E-05	0.90	8.86E-06	0.90
rs761	3	74196	G	A	0.25	.	0.27	NA	NA	29282	5P				
4155		658									PPIAP19	3.97E-05	1.16	1.61E-05	1.15
rs111	10	11632	G	A	.	0.23	.	ABLIM1	intron	AFAP1L2					
96791		3964								AFAP1L2	PPIAP19	3.97E-05	1.16	1.73E-05	1.15
rs290	10	11631	A	G	.	0.23	.	ABLIM1	intron	NAT2	NSAP11	4.21E-05	1.36	1.72E-04	1.39
1044	10	7439	A		.	0.06	.	PSD3	intron						
rs699	8	18594	C	T	.	0.06	.		intron						
6073		558													
rs972	8	18599	C	T	.	0.06	.	PSD3	intron	NAT2	NSAP11	4.30E-05	1.35	1.77E-04	1.38
433		078								LOC6423	LOC1001	4.32E-05	0.94	3.25E-05	0.92
rs249	1	10567	A	G	0.44	.	0.46	NA	NA	37	30867				
1608		3803								KRT18P3	AGPAT6	4.57E-05	1.05	1.45E-05	1.06
rs132	8	41514	A	G	0.17	.	0.13	GINS4	intron	7					
75710		221								C10orf59	LOC3899	4.69E-05	1.10	3.74E-05	1.10
rs127	10	90351	A	G	0.06	0.07	0.06	LIP1	intron	MUC2	LOC1001	5.03E-05	0.99	3.87E-05	1.01
77350		816									32635				
rs659	11	11014	A	G	0.06	0.06	0.07	NA	NA						
7976		74								KLHL34	SMPX	6.06E-05	1.68	2.10E-05	1.71
rs590	X	21604	A	G	.	0.05	.	NA	NA	SLC24A3	RPL12L3	6.46E-05	0.98	5.10E-05	0.97
4577		594													
rs232	20	19713	A	G	.	0.17	.	LOC10013	intron	SLC24A3	RPL12L3	6.46E-05	0.98	5.10E-05	0.97
8452		174													
rs611	20	19710	G	A	.	0.17	.	LOC10013	intron	SLC24A3	RPL12L3	6.46E-05	0.98	5.10E-05	0.97
2574		695													

rs780	75433	A	G						POR	intron	SNORA14 A	TMEM12 OA					
4806	618	A	G	0.32	0.29	.	.	.	.	.	.	.	6.67E-05	0.74	7.41E-05	0.73	
rs457	89230										LOC1001						
9610	980	G	A	0.25	0.26	.	.	.	NA	NA	32348	DAPK1	6.82E-05	0.76	1.25E-04	0.74	
rs546	11239										FYN	WISP3	6.84E-05	1.41	2.61E-05	1.51	
9133	6275	A	G	0.05	.	0.05	.	.	NA	NA							
rs689	11239										FYN	WISP3	6.84E-05	1.41	2.61E-05	1.51	
328	3380	A	G	0.05	.	0.05	.	.	NA	NA							
rs135	74198										LOC1001	HSP90AB					
8206	360	G	A	0.30	.	0.31	.	.	NA	NA	29282	5P	7.03E-05	0.86	3.29E-05	0.87	
rs298	12648										NSMCE2	TRIB1	7.10E-05	-0.70	4.93E-05	-0.70	
0872	6102	A	G	0.47	0.44	0.49	.	.	NA	NA	LOC1001						
rs289	34685										31802	APOL3	7.11E-05	1.16	1.02E-04	1.14	
9258	304	C	A	0.10	.	0.09	.	.	RBM9	intron							
rs575	34641										NDUFA9	LOC1001					
0200	716	C	A	0.10	.	0.09	.	.	RBM9	intron	P1	31802	7.11E-05	1.16	1.02E-04	1.14	
rs339	14032																
429	101	G	A	0.14	0.13	0.16	.	.	NA	NA	DNAH5	TRIO	7.34E-05	0.85	1.20E-04	0.84	
rs117	18900										LOC1001	FAM154					
94832	581	C	T	.	0.22	.	.	.	ADAMTSL1	utr-3	29109	A	7.41E-05	1.24	3.15E-05	1.24	
rs673	15974																
7965	4839	A	G	0.08	.	0.10	.	.	TANC1	intron	BTF3L4P	WDSUB1	7.49E-05	1.00	1.82E-04	-0.96	
rs467	72081											CCDC137					
6847	959	C	T	.	0.15	.	.	.	NA	NA	PROK2	P	7.66E-05	1.15	4.62E-05	1.21	
rs218	12176										LOC6511	LOC7294					
4352	2442	G	A	0.10	0.07	0.07	.	.	NA	NA	44	O2	7.74E-05	0.89	4.98E-05	0.89	
rs755	24323										LOC1001	LOC1001					
2510	4661	A	C	0.09	0.08	0.10	.	.	EFCAB2	intron	29656	28825	7.93E-05	0.93	3.63E-05	0.95	
rs172	13056										LOC1001	LOC1001					
62815	0347	C	T	.	0.14	.	.	.	NA	NA	29525	30376	8.10E-05	1.25	5.66E-05	1.24	
rs110	92880											LOC7294					
20388	11495	A	C	0.18	0.17	0.17	.	.	C11orf75	intron	CCDC67	66	8.12E-05	0.75	4.98E-05	0.77	

rs555	397	11	12534	A	G		0.11	0.07	0.09	CDON	intron	LOC3386 67	LOC7295 61	8.22E-05	0.97	1.66E-04	-0.95
rs187	4797	12	30027	G	A		0.14	0.15	0.16	NA	NA	TMTC1	IP08	8.35E-05	0.80	2.16E-04	0.76
rs119	19628	3	11181	T	G			0.08		NA	NA	LOC4409 73	LOC3891 41	8.48E-05	1.48	1.53E-04	-1.47
rs172	98333	7	25010	A	C			0.31		NA	NA	OSBPL3	CYCS	8.52E-05	0.97	7.04E-05	0.99
rs156	3591	4	18051	G	A		0.10		0.10	NA	NA	LOC3917 19	hCG_202 5798	8.71E-05	1.25	7.35E-05	1.27
rs294	027	11	26485	A	G		0.15		0.19	TMEM16C	intron	LOC6457 05	MUC15	8.77E-05	1.00	3.92E-05	1.02
rs170	17895	2	36029	A	G		0.10	0.09	0.11	NA	NA	MRPL50P 1	CRIM1	8.78E-05	0.88	1.04E-05	0.93
rs688	4748	5	31527	G	A		0.06		0.07	RNASEN	intron	CDH6	C5orf22	8.82E-05	1.13	2.61E-05	1.19
rs688	4823	5	31526	A	G		0.06		0.07	RNASEN	intron	CDH6	C5orf22	8.82E-05	1.13	2.61E-05	1.19
rs275	7491	1	17053	A	G		0.06		0.06	DNM3	intron	LOC1001 28178	LOC1001 31486	8.85E-05	1.10	1.17E-04	-1.08
rs275	7500	1	17054	A	G		0.06		0.06	DNM3	intron	LOC1001 28178	LOC1001 31486	8.85E-05	1.10	1.17E-04	-1.08
rs127	77191	10	95052	G	A		0.14	0.14	0.14	NA	NA	LOC6438 63	FER1L3	9.06E-05	0.77	1.10E-04	0.76
rs957	615	4	23518	T	C			0.10		NA	NA	PPARGC1 A	LOC7291 75	9.22E-05	1.33	5.67E-05	1.36
rs118	98024	2	58115	C	A		0.08		0.10	NA	NA	LOC1001 31953	VRK2	9.24E-05	1.15	6.94E-06	1.25
rs101	69411	2	42491	A	G			0.13		NA	NA	COX7A2L	KCNKG3	9.25E-05	1.16	1.22E-04	-1.14
rs116	93549	2	42543	T	C			0.13		KCNKG3	intron	COX7A2L	LOC1001 29718	9.25E-05	1.16	1.22E-04	-1.14

rs222468	2	42496035	A	G	.	0.13	.	NA	NA	COX7A2L	KCNG3	9.25E-05	1.16	1.22E-04	-1.14
rs222471	2	42491561	G	A	.	0.13	.	NA	NA	COX7A2L	KCNG3	9.25E-05	1.16	1.22E-04	1.14
rs3794002	11	92892707	G	A	0.18	.	0.16	C11orf75	intron	CCDC67	LOC729466	9.29E-05	0.91	6.50E-05	0.95
rs11028782	11	25574425	A	G	0.24	.	0.18	NA	NA	LOC554234	LOC645705	9.40E-05	0.86	1.26E-04	-0.85
rs2076766	13	106979661	A	G	0.18	0.16	0.16	FAM155A	intron	RP11-282A11.1	LIG4	9.43E-05	0.71	1.65E-04	-0.70
rs1871072	10	54571008	A	G	.	0.31	.	NA	NA	MBL2	PCDH15	9.49E-05	1.21	1.42E-04	-1.07
rs6750890	2	208719259	T	G	.	0.10	.	CRYGB	near-gene-5	CRYGB	CRYGA	9.49E-05	1.08	1.93E-04	-1.20
rs6712962	2	23457772	G	A	0.49	0.42	0.45	TRPM8	intron	LOC100130859	SPP2	9.60E-05	-0.70	1.39E-04	-0.69
rs318422	1	82792064	A	G	0.44	0.40	0.41	NA	NA	LPHN2	TTL7	9.70E-05	0.64	1.21E-04	-0.63
rs17182641	14	21146287	G	A	0.11	0.08	0.13	NA	NA	OR10G1P	TRA@	9.71E-05	0.92	1.09E-05	0.97
rs10179237	2	42369005	T	C	.	0.12	.	EML4	intron	SGK493	COX7A2L	9.81E-05	1.19	1.35E-04	-1.18
rs2053349	2	42369709	A	G	.	0.12	.	EML4	intron	SGK493	COX7A2L	9.81E-05	1.19	1.35E-04	-1.18

[0130] Fifty-nine out of 90 variants had the same direction of effect (either reduced or increased risk) in at least two out of the three studies (cutoff $p < 1 \times 10^{-4}$). The top ten most statistically significant variants of that list are shown in Table 5.

Table 5. Ten most statistically significant variants, according to unadjusted p values, associated with grade ≥ 2 proteinuria, hypertension and composite toxicity with the same direction of effect (either reduced or increased risk) in at least two out of three trials for proteinuria and composite toxicity, and three out of four trials for hypertension. *Ch* chromosome, *NA* Intergenic SNP, *MAF* minor allele frequencies in CALGB 80303, 40503, 90401, and 40502 respectively, “_” SNP not present in the genotype platform of the trial, “.” data on proteinuria were not available. Composite toxicity is defined as the occurrence of either proteinuria or hypertension or both.

SNP	Ch	Gene	Feature	Flanking gene	Flanking gene	Base change	MAF	Effect size (β)	p-value
Proteinuria									
rs339947	5	NA	NA	<i>DNAH5</i>	<i>TRIO</i>	C>A	0.12/_/0.14/.	1.27	7.66×10^{-6}
rs12612153	2	<i>C2orf34</i>	Intron	<i>PREPL</i>	<i>LOC100130502</i>	A>C	0.11/_/0.11/.	1.16	3.89×10^{-6}
rs7180310	15	NA	NA	<i>SNORD116-24</i>	<i>SNORD116-25</i>	C>A	0.06/0.05/_/.	1.54	4.10×10^{-6}
rs12482855	21	NA	NA	<i>RIPK4</i>	<i>PRDM15</i>	G>A	0.06/0.06/0.06/.	1.20	6.28×10^{-6}
rs408130	5	NA	NA	<i>DNAH5</i>	<i>TRIO</i>	G>A	0.21/_/0.28/.	1.07	6.33×10^{-6}
rs418173	5	NA	NA	<i>DNAH5</i>	<i>TRIO</i>	G>A	0.21/_/0.28/.	1.07	6.33×10^{-6}
rs7959783	12	NA	NA	<i>MDM1</i>	<i>LOC729376</i>	A>G	0.31/0.26/0.33/.	0.72	7.01×10^{-6}
		<i>LOC33866</i>					0.10/_/0.09/.	1.19	7.49×10^{-6}
rs627761	11	7	Intron	<i>DDX25</i>	<i>CDON</i>	A>G			
rs2688994	3	<i>SLC12A8</i>	Intron	<i>HEG1</i>	<i>ZNF148</i>	G>A	0.13/0.14/0.14/.	0.92	8.13×10^{-6}
rs10486445	7	<i>OSBPL3</i>	Intron	<i>DFNA5</i>	<i>CYCS</i>	A>G	0.42/0.35/0.39/.	0.75	1.17×10^{-5}
Hypertension									
rs13135230	4	NA	NA	<i>CCDC149</i>	<i>LGI2</i>	G>A	0.27/0.28/0.25/0.28	0.46	1.26×10^{-6}
rs2350620	8	<i>ASPH</i>	Intron	<i>hCG_1988300</i>	<i>LOC645551</i>	A>G	0.32/0.26/0.32/0.32	-0.49	1.44×10^{-6}
rs6770663	3	<i>KCNAB1</i>	Intron	<i>LOC751837</i>	<i>SSR3</i>	A>G	0.09/0.09/0.08/0.09	0.57	4.79×10^{-6}
rs1145786	6	NA	NA	<i>MAP3K7</i>	<i>LOC100129847</i>	A>G	0.33/0.32/0.34/0.33	0.39	5.10×10^{-6}
rs7130734	11	NA	NA	<i>LRR4C</i>	<i>LOC100131020</i>	C>A	0.35/0.30/_/0.33	0.42	1.17×10^{-5}
							0.13/0.15/0.14/0.13	0.49	1.99×10^{-5}
rs2179218	20	<i>PTPRT</i>	Intron	<i>LOC643172</i>	<i>PPIAL</i>	G>A	0.44/0.46/0.47/0.47	0.36	2.28×10^{-5}
rs10519829	5	NA	NA	<i>LOC644659</i>	<i>LOC100130551</i>	G>A	0.23/0.19/0.18/0.17	0.43	2.59×10^{-5}
rs1530837	15	<i>PLA2G4E</i>	Intron	<i>EHD4</i>	<i>PLA2G4D</i>	A>G	0.44/0.43/0.50/0.48	-0.37	3.49×10^{-5}
rs2000611	14	<i>KCNK10</i>	Intron	<i>KCNK10</i>	<i>SPATA7</i>	A>G	0.20/0.25/0.23/0.23	0.39	3.74×10^{-5}
rs4611262	12	<i>NUP37</i>	Intron	<i>CCDC53</i>	<i>C12orf48</i>	G>A			
Composite toxicity									
rs11662763	18	NA	NA	<i>LOC645355</i>	<i>TTMA</i>	G>A	0.14/0.11/0.13/.	0.67	9.19×10^{-7}
rs8006648	14	NA	NA	<i>LOC730121</i>	<i>GALC</i>	G>A	0.27/0.28/0.26/.	0.58	2.33×10^{-6}
rs2456761	10	NA	NA	<i>LOC729184</i>	<i>CDC2</i>	C>A	0.35/_/0.34/.	0.72	2.80×10^{-6}
rs1000032	2	NA	NA	<i>KIAA1715</i>	<i>EVX2</i>	C>A	0.13/0.18/0.19/.	0.62	3.21×10^{-6}
rs2687640	7	<i>CPVL</i>	Intron	<i>KIAA0644</i>	<i>LOC100131724</i>	G>A	0.06/_/0.06/.	1.03	3.55×10^{-6}
rs9310707	3	<i>CNTN4</i>	Intron	<i>LOC727810</i>	<i>LOC100130346</i>	G>A	0.37/0.37/0.36/.	0.53	4.03×10^{-6}

rs13156044	5	<i>DNAH5</i>	Intron	<i>LOC391738</i>	<i>TRIO</i>	G>A	0.15/0.11/0.11/.	0.60	8.51×10^{-5}
rs12328055	2	NA	NA	<i>FSHR</i>	<i>LOC130728</i>	G>A	0.06/_/0.05/.	0.99	9.19×10^{-6}
rs4799369	18	<i>DTNA</i>	Intron	<i>LOC646842</i>	<i>MAPRE2</i>	A>G	0.20/0.20/0.18/.	0.59	1.14×10^{-5}
rs2757491	1	<i>DNM3</i>	Intron	<i>LOC100128178</i>	<i>LOC100131486</i>	G>A	0.06/_/0.06/.	0.90	1.21×10^{-5}

[0131] rs339947 (C>A, minor allele frequency, MAF 0.12-0.14) was the most statistically significant ($p=7.66 \times 10^{-8}$, $\beta=1.27$), with the A allele increasing the risk of proteinuria (FIG. 3). rs339947 is an intergenic variant located 73 kb 5' from *DNAH5* and 130 kb 5' from *TRIO* (FIG. 4A). rs408130 and rs418173 (G>A and MAF 0.21-0.28 for both) are among the ten most statistically significant variants and in complete LD with each other ($R^2=1.00$) and in moderate LD with rs339947 ($R^2=0.51$). rs12482855 (G>A, MAF 0.06) had the same direction of effect in all three trials ($p=6.28 \times 10^{-6}$, $\beta=1.20$), with the A allele increasing the risk of proteinuria (FIG. 3). rs12482855 is 4.7 kb 5' from *RIPK4*, an intergenic variant and does not have any variant in high LD ($r^2>0.8$) with it (FIG. 4C).

[0132] For the SNP-based analysis of grade ≥ 3 , the Manhattan and Q-Q plots are shown in FIG. 5. 67 variants were identified as associated with proteinuria. Results are shown in Table 6.

Table 6. SNPs associated with proteinuria (grade ≥3)

SNP	CH	BP	effect allele	reference allele	MAF 80303	MAF 40503	MAF 90401	gene	feature	Flanking gene	Flanking gene	p-value	effect (β)
rs2303028	5	150485987	A	G	0.19	0.20	0.16	ANXA6	intron	TNIP1	CCDC69	5.75E-07	1.57
rs3792775	5	150483530	A	G	0.25	0.24	0.21	ANXA6	intron	TNIP1	CCDC69	1.56E-06	1.49
rs17525472	15	49756960	G	A	0.14	.	0.12	NA	NA	DMXL2	SCG3	2.05E-06	1.98
rs7579312	2	189590930	A	G	.	0.06	.	NA	NA	COL3A1	COL5A2	3.65E-06	2.49
rs7761644	6	6933004	G	A	.	0.08	.	NA	NA	RP11-320C15.1	LOC643936	5.28E-06	1.96
rs6772933	3	136335379	G	A	0.05	0.10	0.07	EPHB1	intron	LOC645218	PPP2R3A	5.31E-06	1.85
rs1018246	2	189879253	G	A	.	0.06	0.06	NA	NA	COL5A2	KRT18P19	5.86E-06	1.68
rs12636883	3	133912212	A	C	0.13	0.13	0.15	NPHP3	intron	UBA5	NCRNA00119	6.57E-06	1.49
rs9502527	6	6930995	G	A	.	0.08	.	NA	NA	RP11-320C15.1	LOC643936	9.56E-06	1.94
rs2070492	3	38332821	A	G	0.09	0.10	0.10	SLC22A14	missense	SLC22A13	XYLB	1.04E-05	1.77
rs7341475	7	103192051	A	G	0.16	0.11	0.15	RELN	intron	SLC26A5	ORC5L	1.07E-05	1.66
rs6434309	2	189591411	A	C	0.08	0.08	0.10	NA	NA	COL3A1	COL5A2	1.22E-05	1.47
rs2105632	11	131842137	G	A	0.14	0.14	0.13	OPCML	intron	HNT	LOC100128095	1.36E-05	1.61
rs1590347	9	10325382	A	G	.	0.12	.	PTPRD	intron	RN7SLP2	LOC646087	1.48E-05	1.90
rs17460569	3	85702141	G	A	0.08	.	0.13	NA	NA	LOC440970	CADM2	1.55E-05	2.33
rs10061011	5	36478917	G	A	.	0.07	0.05	NA	NA	RANBP3L	SLC1A3	1.77E-05	2.57
rs7341301	6	6930714	A	G	0.11	0.08	0.09	NA	NA	RP11-320C15.1	LOC643936	2.20E-05	1.28
rs12248682	10	131200410	A	G	0.09	0.07	0.10	MGMT	intron	hCG_1795091	LOC100129103	2.36E-05	1.65
rs12864893	13	97867240	A	C	0.06	.	0.08	FARP1	intron	RNF113B	STK24	2.56E-05	1.87
rs893911	15	64715542	A	G	0.19	0.14	0.18	NA	NA	LCTL	SMAD6	2.56E-05	1.28
rs280877	16	76215748	G	A	0.19	0.14	0.16	NA	NA	ADAMTS18	NUDT7	2.70E-05	1.22
rs7581769	2	105053248	A	G	0.11	.	0.09	MRPS9	intron	LOC100128684	LOC100133048	2.82E-05	1.62
rs2974319	8	42594234	G	A	0.06	0.08	0.08	NA	NA	C8orf40	CHRN3	2.88E-05	1.92
rs61737465	7	94378463	A	G	.	0.06	.	NA	NA	ARF1P1	PON1	2.89E-05	1.84

rs551112	9	14433468	A	C	0.05	0.09	0.07	NA	NA	NA	NFIB	ZDHC21	2.92E-05	1.61
rs6781294	3	86413784	G	A	0.07	0.12	0.12	NA	NA	NA	CADM2	VGLL3	2.93E-05	1.48
rs1999184	1	176940266	G	A	0.09	.	0.07	NA	NA	NA	C1orf220	LOC646976	3.03E-05	2.29
rs9860570	3	86372146	G	A	0.07	0.12	0.12	NA	NA	NA	CADM2	VGLL3	3.15E-05	1.48
rs9899787	17	62161091	G	A	.	0.10	.	PRKCA	intron	intron	APOH	CACNG5	3.34E-05	2.46
rs7875861	9	10275562	G	A	.	0.08	.	PTPRD	intron	intron	RN7SLP2	LOC646087	3.47E-05	2.87
rs10184895	2	189788608	A	T	.	0.06	.	NA	NA	NA	COL5A2	KRT18P19	3.53E-05	1.67
rs9864170	3	85693598	A	G	0.13	.	0.18	NA	NA	NA	LOC440970	CADM2	3.77E-05	1.68
rs280866	16	76211348	A	G	0.07	0.07	0.07	NA	NA	NA	ADAMTS18	NUDT7	3.87E-05	1.59
rs282999	16	76151802	G	A	0.22	0.17	0.19	NA	NA	NA	ADAMTS18	NUDT7	4.13E-05	1.29
rs9912154	17	62159169	A	G	.	0.11	.	PRKCA	intron	intron	APOH	CACNG5	4.21E-05	2.44
rs4979476	9	116740531	G	A	0.09	0.09	0.08	NA	NA	NA	TNFSF8	TNC	4.26E-05	1.50
rs4916009	1	65144006	A	G	0.08	.	0.09	JAK1	intron	intron	RAVER2	LOC100130270	4.39E-05	1.96
rs1583609	18	26882002	A	G	0.10	0.10	0.11	NA	NA	NA	DSC3	DSC2	4.46E-05	1.72
rs10798628	1	176918995	A	G	0.10	.	0.08	NA	NA	NA	C1orf220	LOC646976	4.76E-05	2.29
rs7826830	8	95723804	A	G	0.17	0.13	0.14	RBM35A	intron	intron	KIAA1429	DPY19L4	5.25E-05	1.36
rs8116164	20	61083073	A	G	0.13	0.08	0.12	NA	NA	NA	LOC100128172	BHLHB4	5.38E-05	1.49
rs12486323	3	133913494	G	A	.	0.16	.	NPHP3	intron	intron	UBA5	NCRNA00119	5.56E-05	1.84
rs9922975	16	26847848	G	A	0.13	0.11	0.12	NA	NA	NA	HS3ST4	C16orf82	5.57E-05	1.27
rs661198	9	10289084	A	G	0.10	0.10	0.09	PTPRD	intron	intron	RN7SLP2	LOC646087	5.61E-05	1.33
rs17717970	5	150954894	G	A	.	0.11	.	NA	NA	NA	FAT2	SPARC	5.79E-05	1.71
rs11965083	6	45935458	G	A	.	0.18	.	NA	NA	NA	RUNX2	CLIC5	5.96E-05	1.80
rs7637944	3	132912301	A	C	0.15	0.14	0.13	CPNE4	intron	intron	MRPL3	LOC729674	5.98E-05	1.26
rs12533538	7	105218549	A	C	0.06	0.06	0.07	ATXN7L1	intron	intron	LOC100131028	LOC100129553	6.14E-05	1.47
rs546913	6	112396275	A	G	0.05	.	0.05	NA	NA	NA	FYN	WISP3	6.73E-05	2.19
rs689328	6	112393380	A	G	0.05	.	0.05	NA	NA	NA	FYN	WISP3	6.73E-05	2.19
rs1332175	9	25493034	G	A	0.07	0.06	0.06	NA	NA	NA	C9orf134	TUSC1	6.78E-05	1.65
rs4479482	20	59037337	A	G	0.11	0.10	0.09	NA	NA	NA	MTCO2L	CDH4	6.98E-05	1.53
rs445775	13	32422448	A	G	.	0.06	0.06	NA	NA	NA	PD55B	hCG_1643176	7.14E-05	1.84

rs10959051	9	10320850	G	A	0.24	0.30	0.22	PTPRD	intron	RN7SLP2	LOC646087	7.23E-05	1.17
rs10516313	4	17028411	A	G	0.14	.	0.16	NA	NA	LOC729006	LOC645097	7.55E-05	1.78
rs7948079	11	96725167	A	G	0.10	0.09	0.08	NA	NA	LOC100131233	LOC643381	7.74E-05	1.29
rs2167171	8	133556707	C	A	0.08	0.09	0.07	KCNQ3	intron	HHLA1	LRRC6	7.77E-05	1.39
rs2277719	18	54350509	A	C	0.06	.	0.07	ALPK2	intron	NEDD4L	LOC100128163	7.79E-05	1.77
rs3844600	10	49353903	A	G	0.22	0.20	0.22	ARHGAP22	intron	MAPK8	WDFY4	7.90E-05	1.23
rs1285295	17	75513707	A	C	.	0.09	.	NA	NA	CBX4	TBC1D16	8.12E-05	1.71
rs2723129	2	23438312	G	A	0.09	0.07	0.09	NA	NA	LOC100130841	KLHL29	8.33E-05	1.33
rs1330656	5	26084219	A	C	0.17	0.17	0.13	NA	NA	MSNL1	LOC100132866	8.68E-05	1.50
rs10065544	5	136592476	G	A	0.20	0.19	0.21	SPOCK1	intron	LOC391834	KLHL3	8.78E-05	1.19
rs992803	3	86325620	A	C	0.14	0.16	0.19	NA	NA	CADM2	VGLL3	8.83E-05	1.20
rs9825532	3	89169850	A	G	.	0.27	.	NA	NA	LOC728432	EPHA3	9.32E-05	2.36
rs2302840	18	41326985	A	G	0.13	.	0.11	NA	NA	LOC100131669	SLC14A2	9.40E-05	1.93
rs17237607	3	126170122	A	G	0.08	0.10	0.08	HEG1	utr-3	MUC13	SLC12A8	9.87E-05	1.36

[0133] Forty-nine out of 67 variants had the same direction of effect (either reduced or increased risk) in at least two out of the three studies (cutoff $p < 1 \times 10^{-4}$). The top ten most statistically significant variants of that list are shown in Table 7. rs2303028 (G>A, MAF 0.16-0.20) was the most statistically significant ($p = 5.75 \times 10^{-7}$, $\beta = 1.57$), with the A allele increasing the risk of proteinuria. rs2303028 is an intronic variant in *ANXA6* (FIG. 6). rs3792775 (G>A and MAF 0.21-0.25) was the next most statistically significant variant ($p = 1.56 \times 10^{-6}$, $\beta = 1.49$), also located in intron of *ANXA6* and in moderate LD with rs2303028 ($R^2 = 0.77$) (FIG. 6), with the A allele increasing the risk of proteinuria. rs12636883 (A>G, MAF 0.05-0.10) also had the same direction of effect in all three trials ($p = 5.57 \times 10^{-6}$, $\beta = 1.49$), with the A allele increasing the risk of proteinuria. rs12636883 is an intronic variant in *NPHP3* (FIG. 6).

Table 7. Ten most statistically significant variants, according to unadjusted p values grade ≥ 3 , associated with proteinuria, hypertension and composite toxicity with the same direction of effect (either reduced or increased risk) in at least two out of three trials for proteinuria and composite toxicity, and three out of four trials for hypertension. *Ch* chromosome, *NA* Intergenic SNP, *MAF* minor allele frequencies in CALGB 80303, 40503, 90401, and 40502 respectively, “_” SNP not present in the genotype platform of the trial, “.” data on proteinuria were not available. Composite toxicity is defined as the occurrence of either proteinuria or hypertension or both.

SNP	Ch	Gene	Feature	Flanking gene	Flanking gene	Base change	MAF	Effect size (β)	p-value
Proteinuria									
rs2303028	5	<i>ANXA6</i>	Intron	<i>TNIP1</i>	<i>CCDC69</i>	G>A	0.19/0.20/0.16/.	1.57	5.75×10^{-7}
rs3792775	5	<i>ANXA6</i>	Intron	<i>TNIP1</i>	<i>CCDC69</i>	G>A	0.25/0.24/0.21/.	1.49	1.56×10^{-6}
rs17525472	15	NA	NA	<i>DMXL2</i>	<i>SCG3</i>	A>G	0.14/_/0.12/.	1.98	2.05×10^{-6}
rs6772933	3	<i>EPHB1</i>	Intron	<i>LOC645218</i>	<i>PPP2R3A</i>	A>G	0.05/0.10/0.07/.	1.85	5.31×10^{-6}
rs10188246	2	NA	NA	<i>COL5A2</i>	<i>KRT18P19</i>	A>G	_/_/0.06/0.06/.	1.68	5.86×10^{-6}
rs12636883	3	<i>NPHP3</i>	Intron	<i>UBA5</i>	<i>NCRNA00119</i>	C>A	0.13/0.13/0.15/.	1.49	5.57×10^{-6}
rs2070492	3	<i>SLC22A14</i>	Missense	<i>SLC22A13</i>	<i>XYLB</i>	G>A	0.09/0.10/0.10/.	1.77	1.04×10^{-5}
rs7341475	7	<i>RELN</i>	Intron	<i>SLC26A5</i>	<i>ORC5L</i>	G>A	0.16/0.11/0.15/.	1.66	1.07×10^{-5}
rs6434309	2	NA	NA	<i>COL3A1</i>	<i>COL5A2</i>	C>A	0.08/0.08/0.10/.	1.47	1.22×10^{-5}
rs2105632	11	<i>OPCML</i>	Intron	<i>HNT</i>	<i>LOC100128095</i>	A>G	0.14/0.14/0.13/.	1.61	1.36×10^{-5}
Hypertension									
rs4782946	16	<i>ATP2C2</i>	Intron	<i>WFDC1</i>	<i>KIAA1609</i>	G>A	0.37/0.38/0.37/0.43	0.66	3.09×10^{-7}
rs17439529	14	<i>AKAP6</i>	Intron	<i>MTCO1P2</i>	<i>NPAS3</i>	G>A	0.36/0.40/0.38/0.40	-0.72	2.08×10^{-6}
rs1530837	15	<i>PLA2G4E</i>	Intron	<i>EHD4</i>	<i>PLA2G4D</i>	A>G	0.23/0.19/0.18/0.17	0.66	4.87×10^{-6}
rs11863271	16	<i>ATP2C2</i>	Intron	<i>WFDC1</i>	<i>KIAA1609</i>	G>A	0.20/0.17/0.19/0.22	0.63	5.23×10^{-6}
rs1171065	13	<i>DCLK1</i>	Intron	<i>NBEA</i>	<i>SOHLH2</i>	A>C	0.19/0.26/0.19/0.21	0.62	5.73×10^{-6}
rs670362	18	NA	NA	<i>VAPA</i>	<i>APCDD1</i>	G>A	0.18/0.14/0.11/0.12	0.67	6.10×10^{-6}
rs2665917	8	<i>NIBP</i>	Intron	<i>C8orf17</i>	<i>LOC100131910</i>	G>A	0.44/0.48/0.47/0.47	0.63	7.13×10^{-6}
rs10967306	9	<i>VLDLR</i>	Intron	<i>FLJ35024</i>	<i>KCNV2</i>	G>A	0.07/0.07/0.09/0.08	0.87	8.16×10^{-6}
rs1320881	8	NA	NA	<i>LOC100132107</i>	<i>ADAM28</i>	G>A	0.24/0.18/0.21/0.24	0.61	9.86×10^{-6}
rs4691370	4	NA	NA	<i>hCG_1814936</i>	<i>PDGFC</i>	A>G	0.06/0.09/_/0.07	0.82	1.00×10^{-5}
Composite toxicity									
rs10867852	9	NA	NA	<i>LOC442427</i>	<i>RASEF</i>	G>A	0.08/0.07/0.06/.	1.16	1.46×10^{-6}
rs7717673	5	<i>SLC25A48</i>	Intron	<i>LOC153328</i>	<i>IL9</i>	G>A	0.11/0.12/0.12/.	0.94	3.93×10^{-6}
rs2454331	8	NA	NA	<i>LOC100129100</i>	<i>RIPK2</i>	A>G	0.43/0.40/0.43/.	-0.77	1.43×10^{-6}
rs873224	8	NA	NA	<i>FLJ43860</i>	<i>LOC100131146</i>	A>G	0.11/0.10/0.08/.	0.86	1.48×10^{-6}
rs966439	14	NA	NA	<i>LOC283584</i>	<i>LOC283585</i>	A>G	0.21/0.17/0.16/.	0.70	1.52×10^{-6}

rs7849777	9	COL5A1	Intron	RXRA	LOC100130622	G>A	0.09/0.05/0.06/.	1.31	1.56x10 ⁻⁶
rs10869538	9	PIP5K1B	Intron	LOC100131240	PRKACG	A>G	0.15/0.16/0.15/.	0.74	1.74x10 ⁻⁶
rs11664759	18	NA	NA	LOC400655	FBXO15	G>A	0.11/0.15/0.15/.	0.83	2.21x10 ⁻⁶
rs1978259	14	NA	NA	LOC283584	LOC283585	C>A	0.20/_/0.16/.	0.81	2.63x10 ⁻⁶
rs17109031	12	NA	NA	SMUG1	LOC100132010	G>A	0.13/0.08/0.10/.	0.85	2.93x10 ⁻⁶

[0134] For the gene-based analysis of grade ≥ 2 , the Q-Q plot is shown in FIG. 7. Identified genes associated with proteinuria, hypertension, and composite toxicity are shown in Table 8.

Table 8. Genes associated with proteinuria, hypertension, or composite toxicity (grade ≥2)

Gene	Proteinuria		Hypertension			Composite toxicity		
	p-value unadjusted	p-value adjusted	Gene	p-value unadjusted	p-value adjusted	Gene	p-value unadjusted	p-value adjusted
<i>C1D</i>	2.00E-08	2.00E-08	<i>UNC50</i>	2.30E-05	3.20E-05	<i>SLC25A24</i>	4.00E-06	3.00E-06
<i>IL17F</i>	1.80E-07	5.90E-07	<i>KATNB1</i>	2.50E-05	7.30E-05	<i>SMS</i>	5.00E-06	5.00E-06
<i>MCM3</i>	5.10E-07	1.15E-06	<i>MGAT4A</i>	4.60E-05	6.10E-05	<i>CEP295</i>	1.00E-05	7.00E-06
<i>SMPX</i>	1.20E-05	8.91E-06	<i>FBXO9</i>	5.10E-05	3.60E-05	<i>YWHAE</i>	1.60E-05	1.30E-05
<i>KLHL34</i>	1.26E-05	1.50E-05	<i>STRIP1</i>	9.80E-05	1.05E-04	<i>PTPN3</i>	4.00E-05	7.10E-05
<i>EAPP</i>	2.70E-05	2.70E-05	<i>CCDC54</i>	1.01E-04	7.70E-05	<i>KLHL35</i>	4.50E-05	3.50E-05
<i>CNKSR2</i>	3.50E-05	2.70E-05	<i>COA5</i>	1.06E-04	1.46E-04	<i>H6PD</i>	5.10E-05	4.00E-05
<i>LIPJ</i>	4.80E-05	7.10E-05	<i>KIFC3</i>	1.18E-04	2.76E-04	<i>MBTPS2</i>	7.50E-05	7.10E-05
<i>ITGB6</i>	5.00E-05	5.50E-05	<i>ICK</i>	1.21E-04	7.70E-05	<i>CRK</i>	1.37E-04	1.51E-04
<i>XCR1</i>	5.70E-05	1.86E-04	<i>AHCYL1</i>	1.45E-04	1.75E-04	<i>SLC17A6</i>	1.50E-04	1.44E-04
<i>RFPL4AL1</i>	1.03E-04	1.42E-04	<i>CAPZA2</i>	1.63E-04	1.36E-04	<i>ALDH4A1</i>	2.13E-04	2.42E-04
<i>PDE3A</i>	1.48E-04	7.86E-04	<i>A4GALT</i>	2.96E-04	1.93E-04	<i>HSD3B2</i>	2.43E-04	2.37E-04
<i>SNX6</i>	1.81E-04	1.11E-04	<i>LUZP4</i>	3.10E-04	2.59E-04	<i>ZNF217</i>	2.74E-04	3.05E-04
<i>PWWP2A</i>	1.82E-04	3.60E-04	<i>CFAP69</i>	3.80E-04	3.21E-04	<i>STAT4</i>	3.44E-04	1.97E-04
<i>NDFIP2</i>	2.01E-04	6.17E-04	<i>STK10</i>	4.30E-04	4.79E-04	<i>TAS1R2</i>	3.46E-04	3.42E-04
<i>VCP</i>	2.09E-04	2.13E-03	<i>TMPPRSS12</i>	5.03E-04	4.01E-04	<i>HDAC11</i>	3.55E-04	4.02E-04
<i>CRYBB2</i>	2.34E-04	9.40E-05	<i>AQP12A</i>	5.12E-04	5.00E-04	<i>AZ12</i>	4.00E-04	4.26E-04
<i>RFPL4A</i>	2.38E-04	2.24E-04	<i>CYSLTR2</i>	5.38E-04	3.81E-04	<i>CMC1</i>	4.26E-04	4.35E-04
<i>CRYBB3</i>	2.47E-04	9.00E-05	<i>DTD1</i>	6.85E-04	5.41E-04	<i>FAM155B</i>	4.36E-04	2.96E-04
<i>ALDH6A1</i>	2.87E-04	3.69E-04	<i>BRD1</i>	6.94E-04	9.23E-04	<i>TGM3</i>	6.14E-04	4.83E-04
<i>CTRB2</i>	3.03E-04	5.53E-04	<i>CSRP2</i>	7.46E-04	7.00E-04	<i>MC3R</i>	6.37E-04	1.07E-03
<i>FANCG</i>	3.12E-04	3.94E-03	<i>FUK</i>	7.74E-04	6.71E-04	<i>IL17F</i>	6.75E-04	5.61E-04
<i>PIGO</i>	3.21E-04	4.29E-03	<i>ST3GAL2</i>	8.16E-04	5.12E-04	<i>HSD3B1</i>	6.93E-04	6.49E-04
<i>KIAA1671</i>	3.29E-04	1.14E-04	<i>CDK14</i>	8.68E-04	8.26E-04	<i>RGPD6</i>	7.04E-04	6.84E-04

DDR2	3.33E-04	1.75E-04	SEPT2	9.21E-04	1.14E-03	RPS3	9.49E-04	1.01E-03
ACP2	3.38E-04	1.99E-04	SF3B3	9.23E-04	6.91E-04	MALL	1.09E-03	7.92E-04
MSANTD1	3.61E-04	4.62E-04	RDH14	9.27E-04	9.37E-04	SPAG4	1.10E-03	1.32E-03
TGFA	3.78E-04	4.88E-04	CCDC58	1.03E-03	7.33E-04	MVH11	1.16E-03	1.47E-03
CTRB1	3.81E-04	6.26E-04	COLGALT2	1.05E-03	8.33E-04	RBL1	1.16E-03	1.43E-03
C9orf131	3.85E-04	1.73E-03	ZDHHC22	1.05E-03	7.83E-04	MRPL9	1.22E-03	1.30E-03
SPRY4	4.63E-04	1.02E-03	NT5C1B	1.10E-03	1.02E-03	SKAP1	1.24E-03	1.58E-03
DIRC2	5.26E-04	2.13E-04	CSTA	1.14E-03	9.29E-04	IFFO2	1.25E-03	1.21E-03
PTGR2	5.43E-04	8.58E-04	IL33	1.16E-03	1.06E-03	C1QTNF7	1.26E-03	7.18E-04
GPX5	6.26E-04	3.13E-04	RYR2	1.20E-03	1.97E-03	GDPD5	1.32E-03	1.11E-03
DNAJB5	6.38E-04	4.62E-04	ACKR3	1.27E-03	8.26E-04	PIK3C2B	1.32E-03	1.03E-03
RGS12	6.72E-04	1.02E-03	EPB41L4B	1.28E-03	1.68E-03	RASGRF1	1.34E-03	1.07E-03
URB2	8.40E-04	4.09E-04	CTSK	1.35E-03	2.17E-03	CCDC172	1.54E-03	1.46E-03
MLH1	8.86E-04	1.38E-03	MFSO2A	1.39E-03	1.48E-03	TMEM182	1.59E-03	1.08E-03
RAN	1.02E-03	1.91E-04	S100P	1.44E-03	1.28E-03	GLRA3	1.76E-03	1.72E-03
FZD6	1.02E-03	1.07E-03	COG4	1.45E-03	1.49E-03	HOMER1	1.88E-03	1.98E-03
TTC1	1.03E-03	9.29E-04	CASR	1.46E-03	1.02E-03	NEFM	1.90E-03	1.60E-03
GNP7	1.04E-03	5.33E-04	CNBD2	1.48E-03	1.19E-03	TET1	2.01E-03	2.22E-03
TAF5L	1.08E-03	5.84E-04	PDE4DIP	1.48E-03	9.00E-04	SLC25A16	2.02E-03	2.01E-03
ZBTB3	1.14E-03	1.75E-04	TIAL1	1.60E-03	1.47E-03	MCM3	2.03E-03	1.87E-03
PITPNM2	1.15E-03	1.39E-03	UBE4B	1.62E-03	1.22E-03	PLCL1	2.03E-03	2.18E-03
CALCR	1.16E-03	1.82E-03	ARNT	1.75E-03	2.47E-03	GABRA3	2.10E-03	2.09E-03
POLR2G	1.18E-03	2.76E-04	ARHGAP4					
SLC25A24	1.21E-03	1.21E-03	2	1.81E-03	1.61E-03	MPP3	2.10E-03	1.93E-03
RWDD2B	1.22E-03	6.29E-04	LRRCSB	1.83E-03	1.42E-03	NPTX2	2.10E-03	2.27E-03
CCT8	1.24E-03	7.50E-04	NYAP2	1.86E-03	1.84E-03	NFS1	2.11E-03	2.48E-03
STOML2	1.32E-03	1.85E-02	SSX5	1.89E-03	2.53E-03	RBM12	2.15E-03	2.09E-03
KRTAP12-4	1.35E-03	1.60E-03	PAQR4	1.93E-03	2.15E-03	SEMA5B	2.26E-03	2.36E-03
			KREMEN2	2.02E-03	2.20E-03	GPATCH2	2.28E-03	1.33E-03

STX2	1.35E-03	2.65E-04	SNX11	2.06E-03	3.48E-03	CPNE1	2.29E-03	2.39E-03
PRB3	1.40E-03	2.34E-03	FLVWCH1	2.07E-03	2.31E-03	PEX11G	2.32E-03	1.93E-03
FER1L6	1.41E-03	2.01E-03	PKMYT1	2.10E-03	2.48E-03	XYLB	2.40E-03	2.87E-03
PRB4	1.45E-03	7.21E-02	PACSN2	2.28E-03	1.79E-03	ADAM12	2.43E-03	1.92E-03
MPP3	1.48E-03	1.08E-03	GP1BA	2.32E-03	1.98E-03	SCYL2	2.43E-03	2.67E-03
OR4N5	1.54E-03	1.82E-03	KIF1A	2.38E-03	1.39E-03	YY2	2.52E-03	2.09E-03
PLEKHB1	1.61E-03	1.06E-03	NBPFF9	2.45E-03	1.79E-03	TMEM165	2.56E-03	2.11E-03
RBM7	1.62E-03	1.51E-03	SKAP1	2.50E-03	3.75E-03	RHAG	2.58E-03	2.42E-03
KRTAP12-3	1.63E-03	2.14E-03	STEAP2	2.50E-03	2.45E-03	ANAPC5	2.61E-03	2.70E-03
FAM214B	1.64E-03	1.83E-02	RBM42	2.52E-03	3.81E-03	CHRG	2.66E-03	2.17E-03
TMEM223	1.74E-03	5.45E-04	TMEM115	2.69E-03	2.31E-03	BIVM	2.73E-03	3.12E-03
PHOSPHO2	1.79E-03	2.85E-03	CIPC	2.70E-03	2.17E-03	CAMKK2	2.78E-03	2.43E-03
NXF1	1.88E-03	5.13E-04	ARFGAP3	2.80E-03	2.01E-03	LMTK3	2.83E-03	2.37E-03
TMEM179B	1.90E-03	5.93E-04	C10orf142	2.83E-03	2.07E-03	C1D	2.92E-03	2.62E-03
OR4M1	1.94E-03	3.15E-03	TTL5	2.91E-03	1.63E-03	DLL3	2.92E-03	2.65E-03
TAF6L	1.99E-03	5.44E-04	PRDM2	2.93E-03	3.37E-03	ERCC5	2.94E-03	3.90E-03
SCYL2	2.02E-03	1.99E-03	ZC2HC1B	3.04E-03	3.48E-03	RBM39	2.97E-03	3.34E-03
GRHL2	2.04E-03	1.01E-02	LTV1	3.10E-03	3.23E-03	TNKS	2.98E-03	3.51E-03
TTC9C	2.04E-03	3.82E-04	CCNI	3.29E-03	3.61E-03	ZNF835	3.07E-03	2.27E-03
DLG5	2.13E-03	1.62E-03	IL23R	3.30E-03	3.29E-03	EIF4E2	3.10E-03	1.94E-03
OR4Q3	2.19E-03	3.31E-03	MRFAP1L1	3.33E-03	3.55E-03	PRPF38A	3.16E-03	2.94E-03
PPP1R16A	2.26E-03	3.27E-03	CLDN9	3.38E-03	4.11E-03	TLK1	3.17E-03	3.19E-03
GCNT2	2.29E-03	1.51E-02	ZBED4	3.45E-03	3.96E-03	TMC1	3.24E-03	2.78E-03
GPT	2.29E-03	3.28E-03	ENO3	3.52E-03	2.97E-03	TRAPPC4	3.28E-03	3.96E-03
MFSD3	2.29E-03	3.23E-03	ZNF774	3.55E-03	3.04E-03	PPP1R15B	3.31E-03	2.80E-03
LARC24	2.32E-03	3.41E-03	SEL1L	3.59E-03	3.43E-03	CCDC84	3.35E-03	3.88E-03
FOXH1	2.33E-03	3.27E-03	NDNF	3.64E-03	2.61E-03	RPS25	3.35E-03	3.69E-03
C11orf71	2.39E-03	1.97E-03	AP2B1	3.76E-03	3.88E-03	KCTD12	3.43E-03	3.24E-03
SIC40A1	2.40E-03	3.24E-03	COX6B1	3.83E-03	4.82E-03	TCOF1	3.45E-03	2.60E-03

RFC3	2.42E-03	3.46E-03	CLDN6	3.97E-03	3.87E-03	SIC37A4	3.49E-03	4.14E-03
RECQL4	2.45E-03	3.25E-03	ETV2	3.97E-03	5.02E-03	TIMM50	3.63E-03	3.14E-03
NCOA3	2.46E-03	1.42E-03	PFN1	3.98E-03	3.33E-03	TIGD1	3.76E-03	2.34E-03
STX5	2.47E-03	6.63E-04	DGKE	4.11E-03	4.43E-03	TRIM28	3.84E-03	3.09E-03
WDR37	2.47E-03	1.75E-03	SLC25A11	4.23E-03	3.71E-03	PDZRN3	3.91E-03	3.97E-03
LGALS2	2.51E-03	9.13E-04	ZNF485	4.23E-03	3.78E-03	KATNB1	3.92E-03	3.13E-03
CYHR1	2.53E-03	3.66E-03	TSPAN33	4.41E-03	3.42E-03	RIIAD1	3.99E-03	4.39E-03
DSG1	2.54E-03	3.00E-03	FBXW11	4.52E-03	6.35E-03	CHMP2A	4.02E-03	2.98E-03
KIFC2	2.54E-03	3.64E-03	IL2	4.52E-03	5.88E-03	MZF1	4.04E-03	3.34E-03
BBS5	2.55E-03	5.94E-03	TBX5	4.55E-03	3.19E-03	UBE2M	4.04E-03	3.17E-03
TONSL	2.56E-03	3.72E-03	C17orf100	4.57E-03	6.94E-03	FBXO47	4.27E-03	4.89E-03
LRRC14	2.58E-03	3.01E-03	XAGE2	4.60E-03	5.24E-03	PGLS	4.49E-03	5.44E-03
REXO2	2.62E-03	3.09E-03	HNMT	4.68E-03	4.21E-03	RALY	4.49E-03	4.18E-03
CCDC173	2.74E-03	2.83E-03	ASPH	4.69E-03	5.83E-03	ZBTB45	4.51E-03	3.64E-03
CYLC1	2.75E-03	2.05E-03	RNF167	4.73E-03	3.72E-03	CTNNB1	4.60E-03	4.57E-03
PCBP2	2.75E-03	5.19E-03	DAB2IP	4.84E-03	4.68E-03	NAMPT	4.73E-03	2.83E-03
SOST	2.79E-03	1.74E-03	KIF1B	4.86E-03	4.48E-03	STAT1	4.77E-03	3.79E-03
DLGAP1	2.82E-03	6.77E-03	CENPL	4.88E-03	2.88E-03	CRISP3	4.81E-03	4.96E-03
SMIM18	2.83E-03	6.26E-04	NUP155	4.88E-03	2.56E-03	PLEKHA6	4.89E-03	4.08E-03
SNRPA	2.84E-03	2.93E-03	ATP10A	4.97E-03	1.06E-02	SLC22A14	4.93E-03	5.34E-03
KLHL41	2.88E-03	6.49E-03	FOXG1	5.02E-03	4.55E-03	CG88	5.05E-03	4.18E-03
RNF19A	2.89E-03	2.69E-03	CRHR2	5.16E-03	5.36E-03	ZNF446	5.08E-03	3.84E-03
EFNA5	2.90E-03	3.64E-03	ZNF707	5.17E-03	4.53E-03	UBC	5.18E-03	3.48E-03
RC3H1	2.94E-03	2.07E-03	HOMER1	5.18E-03	4.44E-03	PTAR1	5.20E-03	2.76E-03
SP1	2.94E-03	1.57E-03	PIM2	5.18E-03	5.38E-03	NPHP1	5.24E-03	5.06E-03
FASTKD1	2.95E-03	6.60E-03	GPAT2	5.32E-03	4.94E-03	TEX13B	5.24E-03	5.56E-03
NUMBL	3.02E-03	2.90E-03	AQP12B	5.38E-03	5.56E-03	IGF1R	5.25E-03	4.61E-03
ZNF256	3.05E-03	2.69E-03	TNFRSF12 A	5.48E-03	6.02E-03	LHB	5.31E-03	3.58E-03

ITPKC	3.12E-03	3.79E-03	CPNE6	5.50E-03	1.24E-02	CD74	5.36E-03	3.92E-03
ACCSL	3.15E-03	7.81E-02	HS6ST1	5.61E-03	1.29E-02	DNAJB5	5.38E-03	6.12E-03
VWA5B1	3.15E-03	3.67E-03	HERC5	5.66E-03	5.20E-03	CITED1	5.39E-03	3.93E-03
DUSP3	3.18E-03	1.79E-03	GPR139	5.69E-03	7.03E-03	KLHL26	5.39E-03	4.53E-03
SERPINC1	3.25E-03	2.56E-03	FLYWCH2	5.73E-03	6.61E-03	C9orf135	5.42E-03	4.63E-03
RNL5	3.26E-03	3.51E-03	TXNDC2	5.76E-03	5.92E-03	ROMO1	5.51E-03	5.81E-03
C19orf54	3.30E-03	3.12E-03	HCFC1R1	5.77E-03	6.77E-03	ZCCHC11	5.55E-03	4.16E-03
ZNF429	3.36E-03	2.88E-03	ZXDA	5.84E-03	7.91E-03	DIRC2	5.59E-03	4.89E-03
C2orf88	3.45E-03	4.75E-03	THOC6	5.85E-03	6.99E-03	DIRAS2	5.62E-03	5.21E-03
KRT25	3.45E-03	3.73E-03	GSTA2	5.94E-03	6.16E-03	AKAP1	5.63E-03	5.12E-03
SHMT1	3.60E-03	2.50E-05	CETP	5.95E-03	5.20E-03	KCNJ14	5.63E-03	5.16E-03
HERC6	3.71E-03	2.85E-03	RIMBP2	5.95E-03	4.68E-03	TXNL1	5.86E-03	3.61E-03
KRTAP10-10	3.74E-03	5.55E-03	C1QTNF7	6.15E-03	5.50E-03	ELOVL2	5.91E-03	8.74E-03
MIA	3.74E-03	4.27E-03	ZNF592	6.21E-03	1.16E-02	ZDHHC7	5.94E-03	3.65E-03
SMCR8	3.81E-03	2.06E-03	GIPC2	6.22E-03	5.12E-03	DUSP3	6.01E-03	6.00E-03
RAB6A	3.82E-03	1.96E-03	ARHGAP1	6.34E-03	5.07E-03	SOST	6.04E-03	6.47E-03
TAS2R42	3.82E-03	5.90E-03	PLAGL1	6.43E-03	6.22E-03	MPZ	6.06E-03	6.28E-03
RBPMS	3.84E-03	1.33E-03	ZNF787	6.44E-03	7.05E-03	COPG2	6.08E-03	5.69E-03
EVPL1	3.88E-03	3.10E-05	ZNF835	6.45E-03	8.13E-03	ETAA1	6.09E-03	7.90E-03
ST6GALNAC 3	3.93E-03	1.03E-02	NAPEPLD	6.46E-03	1.10E-02	NF2	6.11E-03	6.26E-03
RAB4B	4.00E-03	4.65E-03	FAM83H	6.49E-03	5.92E-03	SLC27A5	6.13E-03	5.15E-03
KRTAP10-11	4.06E-03	4.98E-03	CNTF	6.52E-03	7.36E-03	GRWD1	6.23E-03	5.43E-03
OVOL2	4.06E-03	6.26E-03	MAPK15	6.55E-03	5.72E-03	COLGALT 1	6.28E-03	7.51E-03
SLC25A33	4.10E-03	2.97E-03	SMO	6.55E-03	6.00E-03	CTSH	6.32E-03	4.97E-03
WDR1	4.24E-03	5.07E-03	CCDC166	6.68E-03	5.83E-03	CELF3	6.34E-03	5.66E-03
RPLUSD2	4.26E-03	7.35E-04	GOLGA7B	6.69E-03	7.37E-03	FAM129C	6.38E-03	7.67E-03

<i>BOD1L1</i>	4.39E-03	4.92E-03	<i>GATAD1</i>	6.73E-03	8.39E-03	<i>DRC7</i>	6.40E-03	5.35E-03
<i>ID12</i>	4.56E-03	3.28E-03	<i>C3orf38</i>	6.75E-03	6.86E-03	<i>MAP9</i>	6.56E-03	2.67E-03
<i>WDR74</i>	4.59E-03	1.58E-03	<i>ATP1B2</i>	6.79E-03	6.32E-03	<i>VCX2</i>	6.56E-03	5.70E-03
<i>EGIN2</i>	4.66E-03	5.51E-03	<i>MED12</i>	6.83E-03	2.72E-02	<i>YTHDF2</i>	6.60E-03	6.20E-03
<i>ID11</i>	4.68E-03	4.16E-03	<i>URB2</i>	6.83E-03	8.02E-03	<i>OR4M1</i>	6.68E-03	1.16E-02
<i>MED1</i>	4.73E-03	1.80E-03	<i>PCED1B</i>	6.88E-03	9.27E-03	<i>MACROD2</i>	6.70E-03	4.69E-03
<i>MAGEA1</i>	4.82E-03	7.16E-03	<i>MOAP1</i>	6.89E-03	7.75E-03	<i>MAPK15</i>	6.71E-03	5.51E-03
<i>KLHL35</i>	4.83E-03	5.01E-03	<i>NLGN3</i>	6.90E-03	2.77E-02	<i>UGGT1</i>	6.72E-03	1.89E-02
<i>MSTN</i>	4.93E-03	3.60E-03	<i>HAUS5</i>	6.91E-03	8.60E-03	<i>CGB5</i>	6.74E-03	4.91E-03
<i>CLIC4</i>	4.96E-03	9.75E-03	<i>OTOP1</i>	6.97E-03	7.63E-03	<i>PIM3</i>	6.81E-03	6.29E-03
<i>SLC3A2</i>	4.96E-03	1.95E-03	<i>TMEM251</i>	7.05E-03	7.71E-03	<i>GUCD1</i>	6.87E-03	7.38E-03
<i>CYP7B1</i>	5.25E-03	6.55E-03	<i>DARS2</i>	7.08E-03	4.44E-03	<i>KANSL1</i>	6.95E-03	7.57E-03
<i>PTGIS</i>	5.40E-03	6.26E-03	<i>WASF3</i>	7.08E-03	1.10E-02	<i>OR4Q3</i>	6.97E-03	1.12E-02
<i>VPS28</i>	5.43E-03	6.67E-03	<i>RGPD6</i>	7.13E-03	7.15E-03	<i>FAM83H</i>	6.99E-03	5.87E-03
<i>ZNF138</i>	5.47E-03	6.10E-03	<i>MAPK8IP3</i>	7.19E-03	8.33E-03	<i>RNF103</i>	7.08E-03	5.69E-03
<i>RPS10</i>	5.53E-03	4.86E-03	<i>UACA</i>	7.23E-03	9.30E-03	<i>UBXN11</i>	7.16E-03	6.68E-03
<i>SLC30A1</i>	5.61E-03	4.78E-03	<i>GRIPAP1</i>	7.25E-03	7.16E-03	<i>CREB3L3</i>	7.19E-03	9.51E-03
<i>CDC42EP1</i>	5.69E-03	4.23E-03	<i>MEF2D</i>	7.33E-03	6.78E-03	<i>LIPJ</i>	7.30E-03	8.04E-03
<i>HSPA13</i>	5.83E-03	7.30E-03	<i>CRTAC1</i>	7.40E-03	9.06E-03	<i>EFHD1</i>	7.34E-03	5.26E-03
<i>SMIM10L1</i>	5.90E-03	4.24E-03	<i>OR5M1</i>	7.59E-03	5.59E-03	<i>SATL1</i>	7.34E-03	5.24E-03
<i>BANP</i>	6.22E-03	8.91E-03	<i>ZFP91</i>	7.61E-03	5.47E-03	<i>IZUMO2</i>	7.43E-03	7.49E-03
<i>CDK2AP1</i>	6.28E-03	7.38E-03	<i>TUBGGCP3</i>	7.62E-03	9.74E-03	<i>CGB1</i>	7.49E-03	5.21E-03
<i>IRF5</i>	6.31E-03	7.71E-03	<i>CERS5</i>	7.70E-03	9.45E-03	<i>LARP1B</i>	7.49E-03	6.48E-03
<i>NXPH3</i>	6.32E-03	8.94E-03	<i>GSTP1</i>	7.74E-03	8.33E-03	<i>CGB2</i>	7.56E-03	5.27E-03
<i>SULT1C2</i>	6.40E-03	6.67E-03	<i>HEY1</i>	7.93E-03	1.00E-02	<i>KLF14</i>	7.65E-03	5.81E-03
<i>BIRC7</i>	6.45E-03	1.08E-02	<i>BLOC1S4</i>	8.04E-03	7.91E-03	<i>CYTH2</i>	7.67E-03	7.05E-03
<i>KPNA3</i>	6.51E-03	1.72E-03	<i>CLIC6</i>	8.06E-03	7.77E-03	<i>MAP3K7</i>	7.68E-03	8.11E-03
<i>FGFR1OP</i>	6.57E-03	1.86E-03	<i>RGL4</i>	8.22E-03	1.89E-02	<i>TTL110</i>	7.71E-03	6.72E-03

PA5D1	6.58E-03	7.01E-03	WFIKN2	8.30E-03	6.80E-03	ZNF707	7.71E-03	6.07E-03
ABCBI0	6.64E-03	5.38E-03	HSD3B1	8.45E-03	9.51E-03	PPP2R1A	7.73E-03	5.78E-03
NKAIN4	6.65E-03	1.10E-02	SPAG4	8.49E-03	7.10E-03	HSPA13	7.77E-03	8.48E-03
DSG4	6.81E-03	9.69E-03	11-Sep	8.62E-03	9.72E-03	NBPF4	7.77E-03	7.72E-03
NKX3-2	6.82E-03	4.65E-03	SST	8.64E-03	1.15E-02	PAIP2	7.86E-03	8.55E-03
AMHR2	6.86E-03	4.81E-03	UPK1A	8.86E-03	8.32E-03	SCAND1	7.91E-03	8.12E-03
PRR13	6.90E-03	5.07E-03	ADAMTS2 0	8.93E-03	8.28E-03	DHRS7	7.99E-03	7.25E-03
OGT	6.93E-03	7.99E-03	CXCL3	8.94E-03	9.32E-03	NCL	8.02E-03	7.61E-03
MROH9	6.95E-03	9.50E-03	C17orf67	8.98E-03	1.07E-02	KRT25	8.05E-03	8.57E-03
A1CF	7.00E-03	6.01E-03	WDR87	8.99E-03	9.91E-03	GPR63	8.08E-03	8.11E-03
MAPT	7.12E-03	7.20E-03	TOB1	9.37E-03	5.88E-03	ALPK2	8.21E-03	7.95E-03
MFHAS1	7.12E-03	1.86E-02	BCAR1	9.47E-03	7.97E-03	CABP5	8.23E-03	9.68E-03
TAF1	7.13E-03	8.69E-03	CPNE4	9.48E-03	1.34E-02	HES7	8.23E-03	9.19E-03
ATG101	7.28E-03	6.35E-03	MGARP	9.55E-03	1.06E-02	DEFB112	8.24E-03	9.00E-03
TOP3A	7.37E-03	4.99E-03	TERT	9.55E-03	6.65E-03	PCGF6	8.26E-03	7.65E-03
EFHB	7.44E-03	6.63E-03	FMOD	9.67E-03	5.49E-03	ORC1	8.32E-03	7.96E-03
NR1H3	7.46E-03	5.63E-03	LYPD3	9.68E-03	9.51E-03	CD300LG	8.52E-03	8.06E-03
PET117	7.52E-03	7.36E-03	SUC1A2	9.71E-03	8.49E-03	NEFL	8.60E-03	7.96E-03
PIIG	7.57E-03	1.95E-02	TNMD	9.72E-03	9.27E-03	HNRNPD	8.61E-03	8.20E-03
DAZAP2	7.66E-03	4.69E-03	NREP	9.86E-03	8.78E-03	STAG2	8.64E-03	7.66E-03
PPP1R14D	7.78E-03	3.53E-03	FBXO3	9.91E-03	6.76E-03	FBR5	8.82E-03	8.84E-03
ZFYVE19	7.85E-03	3.07E-03	STON1	9.97E-03	9.49E-03	CC2D2A	8.88E-03	7.08E-03
SNTG1	7.89E-03	8.43E-03	HTRA3	9.99E-03	1.03E-02	CCDC166	8.94E-03	7.44E-03
PRP51	7.94E-03	8.51E-03				CFAP69	8.98E-03	8.17E-03
SIC36A4	7.95E-03	5.05E-03				TFB1M	9.12E-03	1.16E-02
SMAGP	8.02E-03	4.61E-03				C14orf17 7	9.17E-03	8.13E-03
CD300LG	8.10E-03	7.00E-03				IQCA1	9.17E-03	8.03E-03

CTXN2	8.11E-03	1.02E-02							MROH8	9.20E-03	8.00E-03
ZSWIM6	8.17E-03	1.52E-03							AUTS2	9.21E-03	7.21E-03
KRTAP10-12	8.24E-03	1.05E-02							SMG1	9.26E-03	1.06E-02
PRRG3	8.26E-03	7.78E-03							NSUN3	9.32E-03	9.80E-03
DEPDC4	8.30E-03	6.83E-03							SSBP3	9.38E-03	1.02E-02
CTHRC1	8.34E-03	1.36E-02							ING3	9.47E-03	1.18E-02
C19orf18	8.39E-03	7.28E-03							SND1	9.50E-03	7.05E-03
KRTAP12-1	8.42E-03	1.04E-02							KPNA3	9.51E-03	5.29E-03
SOC54	8.44E-03	5.01E-03							NCALD	9.55E-03	1.10E-02
PLSCR5	8.48E-03	1.18E-02							TERT	9.55E-03	7.97E-03
AVP	8.58E-03	5.39E-03							KLF3	9.56E-03	1.09E-02
NR2E1	8.69E-03	2.43E-02							UBN2	9.74E-03	9.79E-03
C4orf36	8.79E-03	7.50E-03							ZFP37	9.76E-03	6.02E-03
GNGL1	8.83E-03	1.04E-01							GPI	9.80E-03	1.03E-02
MANSC1	8.83E-03	1.10E-02							ODF1	9.84E-03	8.11E-03
YTHDF1	8.91E-03	1.08E-02							HIST2H2B F	9.98E-03	9.42E-03
MUC5AC	9.02E-03	2.03E-02									
GTPBP4	9.10E-03	6.79E-03									
SEMA5B	9.11E-03	6.34E-03									
ZNF410	9.13E-03	1.16E-02									
MADD	9.28E-03	6.45E-03									
ETNPPL	9.30E-03	5.88E-03									
ATP1A1	9.31E-03	2.53E-02									
FREM3	9.35E-03	6.61E-03									
SLC22A2	9.40E-03	1.04E-02									
SLC25A26	9.41E-03	2.16E-02									
KRTAP12-2	9.42E-03	1.21E-02									
FBN1	9.43E-03	1.05E-02									

[0135] The ten most statistically significant genes are shown in Table 9. *C1D* ($p=2.00 \times 10^{-8}$) was the most significant, followed by *IL17F* ($p=1.80 \times 10^{-7}$).

Table 9. Ten most statistically significant genes, according to unadjusted p values, associated with proteinuria, hypertension, and composite toxicity from the gene-based association analysis grade ≥ 2 . Composite toxicity is defined as the occurrence of either proteinuria or hypertension or both.

Proteinuria		Hypertension		Composite toxicity	
Gene	p-value	Gene	p-value	Gene	p-value
<i>C1D</i>	2.00×10^{-8}	<i>UNC50</i>	2.30×10^{-5}	<i>SLC25A24</i>	4.00×10^{-6}
<i>IL17F</i>	1.80×10^{-7}	<i>KATNB1</i>	2.50×10^{-5}	<i>SMS</i>	5.00×10^{-6}
<i>MCM3</i>	5.10×10^{-7}	<i>MGAT4A</i>	4.60×10^{-5}	<i>CEP295</i>	1.00×10^{-5}
<i>SMPX</i>	1.20×10^{-5}	<i>FBXO9</i>	5.10×10^{-5}	<i>YWHA</i>	1.60×10^{-5}
<i>KLHL34</i>	1.26×10^{-5}	<i>STRIP1</i>	9.80×10^{-5}	<i>PTPN3</i>	4.00×10^{-5}
<i>EAPP</i>	2.70×10^{-5}	<i>CCDC54</i>	1.01×10^{-4}	<i>KLHL35</i>	4.50×10^{-5}
<i>CNKSR2</i>	3.50×10^{-5}	<i>COA5</i>	1.06×10^{-4}	<i>H6PD</i>	5.10×10^{-5}
<i>LIPJ</i>	4.80×10^{-5}	<i>KIFC3</i>	1.18×10^{-4}	<i>MBTPS2</i>	7.50×10^{-5}
<i>ITGB6</i>	5.00×10^{-5}	<i>ICK</i>	1.21×10^{-4}	<i>CRK</i>	1.37×10^{-4}
<i>XCR1</i>	5.70×10^{-5}	<i>AHCYL1</i>	1.45×10^{-4}	<i>SLC17A6</i>	1.50×10^{-4}

Variants and genes associated with bevacizumab-induced hypertension

[0136] For the SNP-based analysis of grade ≥ 2 hypertension, the Manhattan and Q-Q plots are shown in FIG. 2. 104 variants associated with hypertension were identified (Table 10).

Table 10. SNPs associated with hypertension (grade 22).

SNP	C	H	BP	effect allele	reference allele	MA F 803 03	MA F 405 03	MA F 904 01	MA F 405 02	gene	feature	Flanking gene	Flanking gene	p-value unadjusted	effect (β) unadjusted	p-value adjusted	effect (β) adjusted
rs3793027	6	70727823		G	A	0.09	.	.	.	COL19A1	intron	LMBRD1	COL9A1	1.21E-06	1.87	4.12E-06	2.00
rs13135230	4	24605796		A	G	0.27	0.28	0.25	0.28	NA	NA	CCDC149	LG12	1.26E-06	0.46	1.36E-06	0.47
rs2350620	8	62660161		G	A	0.32	0.26	0.32	0.32	ASPH	intron	hCG_1988300	LOC645551	1.44E-06	-0.49	1.23E-06	-0.50
rs7204266	1	9876004		G	A	0.28	.	0.28	.	GRIN2A	intron	LOC653737	LOC727844	3.61E-06	0.76	2.58E-06	0.79
rs6770663	3	157514872		G	A	0.09	0.09	0.08	0.09	KCNAB1	intron	LOC751837	SSR3	4.79E-06	0.57	4.16E-06	0.58
rs1145786	6	91678597		G	A	0.33	0.32	0.34	0.33	NA	NA	MAP3K7	LOC100129847	5.10E-06	0.39	7.18E-06	0.39
rs7038808	9	91931116		A	G	0.13	.	0.15	.	NA	NA	IL6RL1	OR7E31P	5.20E-06	0.91	9.36E-06	0.90
rs11036390	1	41387322		C	A	.	0.27	.	0.31	NA	NA	LRR4C	LOC100131020	5.23E-06	0.46	5.57E-06	0.47
rs10905087	1	70822760		A	G	.	0.25	.	0.23	NA	NA	LOC439949	SFM/BT2	6.01E-06	-0.64	5.30E-06	-0.65
rs12316952	1	46238282		G	A	0.06	.	0.08	.	NA	NA	LOC100127978	RPAP3	6.17E-06	1.14	8.30E-06	1.14
rs17097718	1	98252288		T	C	.	0.06	.	.	C14orf177	missense	LOC100132612	RPL3P4	8.56E-06	1.48	8.45E-03	-0.54
rs757354	1	46233814		C	A	0.06	.	0.08	.	NA	NA	LOC100127978	RPAP3	1.11E-05	1.11	1.42E-05	1.11
rs7553399	1	3406309		C	A	.	0.25	.	.	MEGF6	missense	ARHGEF16	TPRG1L	1.14E-05	1.06	1.34E-05	1.06

rs71307 34	1 1	4138593 1	A	C	0.35	0.30	.	0.33	NA	NA	NA	LRR4C	LOC10013 1020	1.17E- 05	0.42	8.77E- 06	0.43
rs13176 984	5	1516537 39	C	T	.	0.11	.	0.18	NA	NA	NA	GLRA1	NMUR2	1.20E- 05	0.55	6.10E- 06	0.57
rs11714 367	3	1767141 80	A	G	0.14	.	0.17	.	NAALAD12	intron	intron	LOC64721 2	LOC10012 8870	1.40E- 05	0.83	1.49E- 05	0.82
rs21792 18	2 0	4050287 4	A	G	0.13	0.15	0.14	0.13	PTPRT	intron	intron	LOC64317 2	PPIAL	1.99E- 05	0.49	3.00E- 05	0.48
rs16986 558	2 0	4020782 4	A	G	0.06	.	0.06	.	PTPRT	intron	intron	LOC64317 2	PPIAL	2.18E- 05	0.93	1.02E- 05	0.99
rs10519 829	5	1250453 25	A	G	0.44	0.46	0.47	0.47	NA	NA	NA	LOC64465 9	LOC10013 0551	2.28E- 05	0.36	1.84E- 05	0.37
rs15308 37	1 5	4006908 2	G	A	0.23	0.19	0.18	0.17	PLA2G4E	intron	intron	EHD4	PLA2G4D	2.59E- 05	0.43	2.28E- 05	0.44
rs46972 73	4	2184489 4	A	G	.	0.28	.	0.20	NA	NA	NA	KCNIP4	GPR125	2.60E- 05	0.50	3.76E- 05	0.49
rs29499 29	1 7	6294307 6	T	C	.	0.27	.	0.25	PITPNC1	intron	intron	LOC72982 2	NOL11	2.98E- 05	0.48	3.75E- 05	0.48
rs15644 70	8	1362901 17	A	C	0.30	.	0.32	.	NA	NA	NA	ZFAT	LOC28609 4	3.10E- 05	0.74	2.70E- 05	0.75
rs72019 30	1 6	9866156 17	G	A	0.29	.	0.33	.	GRIN2A	intron	intron	LOC65373 7	LOC72784 4	3.15E- 05	0.72	2.35E- 05	0.74
rs21259 44	4	4242167 5	A	G	0.08	.	0.10	.	NA	NA	NA	ATP8A1	GRXCR1	3.19E- 05	0.86	5.09E- 05	0.84
rs10828 545	1 0	1866960 9	A	G	.	0.34	.	0.37	CACNB2	intron	intron	SLC39A12	NSUN6	3.21E- 05	-0.47	1.79E- 05	-0.49
rs46880 81	3	1193981 44	G	A	.	0.41	.	0.40	NA	NA	NA	LOC72887 3	IGSF11	3.38E- 05	-0.44	4.05E- 05	-0.44
rs99215 41	1 6	9899263 4	A	C	0.23	.	0.24	.	GRIN2A	intron	intron	LOC65373 7	LOC72784 4	3.38E- 05	0.71	3.17E- 05	0.72
rs48999 47	1 4	0.88769 467	C	T	.	0.36	.	0.32	KCNK10	intron	intron	KCNK10	SPATA7	3.48E- 05	0.44	1.75E- 05	0.45

rs20006 11	1 4	8783707 9	G	A	0.44	0.43	0.50	0.48	KCNK10	intron	KCNK10 9137	SPATA7	3.49E- 05	-0.37	2.25E- 05	-0.38
rs11732 343	4	8972291 4	A	G	0.08	.	.	.	NA	NA	LOC10012 9137	HERC3	3.62E- 05	1.70	2.22E- 05	1.78
rs46112 62	1 2	1010268 89	A	G	0.20	0.25	0.23	0.23	NUP37	intron	CCDC53	C12orf48	3.74E- 05	0.39	1.59E- 05	0.40
rs95123 28	1 3	2614980 3	G	A	0.06	0.09	0.09	0.08	WASF3	intron	LOC64652 7	GPR12	3.84E- 05	0.54	8.30E- 05	0.52
rs99678 4	3	1647073 01	T	G	.	0.23	.	0.27	NA	NA	LOC64710 7	LOC73012 9	3.86E- 05	0.45	5.91E- 05	0.44
rs13161 952	5	1250464 94	G	A	.	0.30	.	0.21	NA	NA	LOC64465 9	LOC10013 0551	3.96E- 05	0.45	2.11E- 05	0.46
rs15175 27	2	2062525 47	A	G	0.41	.	0.42	.	NA	NA	PARD3B	NRP2	4.11E- 05	0.69	7.39E- 05	0.68
rs76012 2	2 1	4070161 6	A	G	0.23	.	0.26	.	DSCAM	intron	PCP4	BACE2	4.15E- 05	0.69	7.05E- 05	0.69
rs11713 383	3	6352390 0	A	G	0.38	.	0.35	.	SYNPR	intron	LOC10012 9031	S100A1L	4.17E- 05	0.71	7.36E- 05	0.71
rs99338 32	1 6	9856135	A	G	0.29	.	0.32	.	GRIN2A	intron	LOC65373 7	LOC72784 4	4.19E- 05	0.70	3.09E- 05	0.73
rs13501 17	4	3466675 2	G	A	0.40	0.33	0.38	0.39	NA	NA	LOC72781 9	LOC10013 2690	4.32E- 05	-0.39	3.35E- 05	-0.40
rs22207 06	9	1046737 84	G	A	0.05	.	0.06	0.07	NA	NA	LOC10013 1879	CYLC2	4.40E- 05	0.65	6.89E- 05	0.64
rs17648 695	1 1	1003636 35	C	T	.	0.14	.	0.11	LOC10012 9602	intron	FLJ32810	TMEM133	4.41E- 05	0.54	3.70E- 05	0.55
rs17654 410	1 1	1003693 56	T	C	.	0.14	.	0.11	TMEM133	utr-3	LOC10012 9602	PGR	4.41E- 05	0.54	3.70E- 05	0.55
rs24567 61	1 0	6220054 8	A	C	0.35	.	0.34	.	NA	NA	LOC72918 4	CDC2	4.57E- 05	0.74	5.35E- 05	0.74
rs77380 87	6	939790	G	A	0.42	0.40	0.37	0.37	NA	NA	EXOC2	FOXQ1	4.67E- 05	0.36	6.59E- 05	0.36

rs17787479	8	140579876	A	C		0.21	0.26	0.20	0.20	NA	NA	COL22A1	KCNK9	4.68E-05	0.40	5.88E-05	0.40
rs7618831	3	63531349	A	G		0.38	.	0.36	.	SYNPR	intron	LOC100129031	S100A1L	4.69E-05	0.71	8.08E-05	0.70
rs873766	2	106042957	C	T		.	0.12	.	0.10	NA	NA	LOC100132455	C2orf40	4.71E-05	0.57	5.40E-05	0.57
rs2886725	5	37770836	A	G		.	0.14	.	.	NA	NA	WDR70	GDNF	4.80E-05	1.02	6.25E-05	1.07
rs10087981	8	23282409	A	C		.	0.32	.	0.28	LOXL2	intron	R3HCC1	ENTPD4	4.84E-05	-0.49	6.10E-05	-0.49
rs6302	6	87782302	T	C		.	0.10	.	0.08	HTR1E	refere nce	LOC643971	CGA	4.85E-05	0.63	8.23E-05	0.61
rs365277	13	61808609	G	A		0.47	0.46	0.41	0.45	NA	NA	LOC100133193	LOC647259	4.93E-05	-0.37	6.04E-05	-0.37
rs3858416	11	100230559	T	C		.	0.06	.	0.05	FLJ32810	intron	LOC100128386	LOC100129602	4.95E-05	0.66	3.14E-05	0.68
rs7821773	8	9748866	G	A		0.08	0.05	0.08	.	NA	NA	TNKS	MSRA	4.97E-05	0.78	2.07E-03	0.46
rs10842185	12	23625382	G	A		0.10	0.13	0.10	0.10	SOX5	intron	LOC100131418	LOC100129937	4.97E-05	0.50	2.92E-05	0.52
rs6445360	3	63523420	A	G		0.38	.	0.36	.	SYNPR	intron	LOC100129031	S100A1L	5.26E-05	0.71	9.10E-05	0.70
rs2825322	21	19343047	G	A		0.27	0.34	0.27	0.26	NA	NA	PPIAL3	SLC6A6P	5.51E-05	-0.43	5.98E-05	-0.43
rs805772	20	5619460	T	G		.	0.13	.	0.12	NA	NA	RP5-1022P6.2	C20orf196	5.58E-05	0.57	5.50E-05	0.58
rs1352981	9	104625739	G	A		0.08	.	0.08	.	NA	NA	LOC100131879	CYLC2	5.74E-05	0.85	6.63E-05	0.85
rs12170867	22	30292076	A	G		.	0.09	.	0.11	SFI1	intron	LOC100128535	PISD	5.76E-05	0.57	8.56E-05	0.56
rs2278495	18	52838811	A	G		0.25	.	0.24	.	WDR7	intron	LOC100130858	FAM44C	6.11E-05	0.72	8.93E-05	0.71

rs2729007	3	2132357	A	G	0.21	0.26	0.22	0.22	CNTN4	intron	LOC727810	LOC100130346	6.14E-05	0.40	8.80E-05	0.39
rs2991492	13	78625387	A	G	.	0.48	.	0.48	NA	NA	LOC390415	LOC100128339	6.15E-05	-0.43	9.05E-05	-0.42
rs2267796	16	9884214	C	A	0.24	.	0.24	.	GRIN2A	intron	LOC653737	LOC727844	6.60E-05	0.69	5.78E-05	0.70
rs2232030	4	24614069	G	A	0.15	0.18	0.13	0.15	LG12	utr-3	CCDC149	SEPSECS	6.67E-05	0.46	7.23E-05	0.47
rs7659172	4	24609653	A	G	.	0.18	.	0.15	NA	NA	CCDC149	LG12	6.83E-05	0.53	9.37E-05	0.53
rs1171566	1	154766593	C	T	.	0.28	.	0.32	IQGAP3	refere nce	MEF2D	TTC24	6.84E-05	0.41	7.42E-05	0.41
rs1370215	18	52839937	G	A	0.25	.	0.24	.	WDR7	intron	LOC100130858	FAM44C	6.99E-05	0.72	1.02E-04	0.70
rs540509	7	17071448	G	A	.	0.19	.	0.23	NA	NA	LOC100131425	LOC100131512	7.03E-05	0.45	4.91E-05	0.46
rs1288934	1	224894661	G	A	0.24	0.27	0.24	0.26	ITPKB	intron	C1orf95	PSEN2	7.05E-05	-0.43	7.60E-05	-0.43
rs3745539	19	56219853	A	G	0.08	.	0.06	.	KLK11	missen se	KLK10	KLK12	7.08E-05	0.93	7.94E-05	0.92
rs2860529	4	105672170	G	A	0.22	0.20	0.23	0.23	NA	NA	LOC728847	LOC391679	7.11E-05	0.37	8.67E-05	0.37
rs2172102	5	125024395	G	A	.	0.28	.	0.19	NA	NA	LOC644659	LOC100130551	7.12E-05	0.44	5.08E-05	0.45
rs1219508	10	123451644	A	G	0.22	0.24	0.23	0.23	NA	NA	LOC729426	ATE1	7.14E-05	-0.46	1.42E-04	0.44
rs4580675	4	80827274	A	G	0.43	0.47	0.44	0.47	NA	NA	OR7E94P	GDEP	7.15E-05	-0.36	8.47E-05	-0.36
rs12480201	20	59812166	A	G	0.14	.	0.15	.	CDH4	intron	LOC100131417	TAF4	7.18E-05	0.85	4.39E-05	0.88
rs1268663	14	64335834	A	G	0.20	0.22	0.20	0.21	SPTB	intron	LOC100129913	CHURC1	7.34E-05	0.41	5.26E-05	0.42

rs47756 10	1 5	6111911 0	A	G	.	0.31	.	0.28	NA	NA	TLN2	TPM1	7.37E- 05	0.42	7.35E- 05	0.42
rs11133 274	4	5399413 7	A	G	0.21	0.20	0.21	0.20	FIP1L1	intron	LOC10013 0982	LNx1	7.50E- 05	0.38	2.46E- 05	0.41
rs48138 86	2 0	912652	G	A	0.11	0.12	0.12	0.12	RSPO4	intron	ANGPT4	PSMF1	7.61E- 05	0.46	5.87E- 05	0.47
rs47435 99	9	1046517 78	G	A	0.08	.	0.08	.	NA	NA	LOC10013 1879	CYLC2	7.73E- 05	0.84	9.03E- 05	0.84
rs27132 89	4	1347598 43	A	G	0.48	0.49	0.49	0.47	NA	NA	PCDH10	PABPC4L	7.89E- 05	0.34	8.57E- 05	0.34
rs18841 14	2 0	914504	T	G	.	0.08	.	0.08	RSPO4	intron	ANGPT4	PSMF1	7.90E- 05	0.62	5.11E- 05	0.64
rs33824 8	1	5870389 3	C	A	0.29	0.24	0.27	0.29	NA	NA	DAB1	OMA1	7.90E- 05	0.37	8.49E- 05	0.37
rs37678 67	1	2106242 22	G	A	0.35	.	0.38	.	TMEM206	intron	PPP2R5A	NENF	7.91E- 05	-0.81	1.00E- 04	-0.80
rs95304 88	1 3	7537015 6	A	G	0.36	.	0.42	.	NA	NA	FLJ35379	LOC10013 2423	8.04E- 05	0.68	1.49E- 04	-0.66
rs11251 166	1 0	2357939	C	A	.	.	.	0.28	NA	NA	LOC72820 9	LOC72787 8	8.22E- 05	0.50	7.30E- 05	0.51
rs14522 32	1 2	8375036 2	C	A	0.37	.	0.37	.	NA	NA	LOC10012 8335	SLC6A15	8.38E- 05	0.69	1.03E- 04	0.69
rs76675 10	4	4191390 3	G	A	.	0.15	.	0.15	NA	NA	BEND4	SHISA3	8.39E- 05	0.49	9.27E- 05	0.49
rs26876 40	7	2913878 1	A	G	0.06	.	0.06	0.05	CPVL	intron	KIAA0644	LOC10013 1724	8.45E- 05	0.66	9.57E- 05	0.66
rs71127 2	6	9166745 4	A	G	0.28	0.27	0.30	0.27	NA	NA	MAP3K7	LOC10012 9847	8.72E- 05	0.35	8.10E- 05	0.36
rs16924 767	1 2	2226083 4	G	A	0.13	.	0.16	.	ST8SIA1	intron	CMA5	KIAA0528	8.98E- 05	0.89	9.26E- 05	0.90
rs12757 197	1	2336571 82	A	G	0.07	.	0.10	.	TBCE	intron	GGPS1	B3GALNT2	9.19E- 05	0.83	4.07E- 05	0.91

rs11164023	1	84861990	G	A	0.20	0.17	0.19	0.22	NA	NA	CTBS	C1orf180	9.25E-05	0.40	5.75E-05	0.41
rs4948291	105	59770095	T	C	.	0.33	.	0.36	UBE2D1	intron	CISD1	TFAM	9.30E-05	0.40	7.00E-05	0.41
rs17156773	10	1740763	A	G	.	0.07	.	0.09	ADARB2	intron	C10orf109	LOC100129465	9.42E-05	0.63	8.49E-05	0.64
rs2288502	5	156582630	A	G	0.07	0.07	0.06	0.06	ITK	intron	FAM71B	CYFIP2	9.45E-05	0.61	1.04E-04	-0.61
rs1362972	12	94599424	A	C	0.12	.	0.18	.	NTN4	intron	LOC100132594	SNRPF	9.47E-05	0.79	1.73E-04	-0.78
rs1480802	8	136293393	C	A	0.37	.	0.38	.	NA	NA	ZFAT	LOC286094	9.54E-05	0.71	6.70E-05	0.73
rs6681946	1	17358138	G	A	0.20	.	0.21	.	NA	NA	PADI2	LOC400743	9.59E-05	0.73	1.18E-04	0.72
rs4735993	8	1141126	G	A	.	0.27	.	0.26	NA	NA	LOC401442	DLGAP2	9.70E-05	0.42	4.38E-05	0.45
rs2515034	8	119565108	G	A	0.06	.	.	.	SAMD12	intron	EXT1	LOC441377	9.86E-05	1.68	7.67E-05	1.77
rs4691370	4	157809201	G	A	0.06	0.09	.	0.07	NA	NA	hCG_1814936	PDGFC	9.91E-05	0.59	1.02E-04	0.60
rs2077923	16	9788282	G	A	0.29	.	0.32	.	GRIN2A	intron	LOC653737	LOC727844	9.95E-05	0.68	8.64E-05	0.69

[0137] Thirty-four out of the 104 variants had the same direction of effect in at least three out of the four studies (cutoff $p < 1 \times 10^{-4}$). The top ten most statistically significant variants of that list are shown in **Table 5**. rs13135230 (G>A, MAF 0.25-0.28) was the most statistically significant ($p = 1.26 \times 10^{-6}$, $\beta = 0.46$), with the A allele increasing the risk of hypertension (**FIG. 3**). rs13135230 is 3.8 kb 3' from *LGI2* (**FIG. 4B**). rs2350620 (A>G, MAF 0.26-0.32) is the next most statistically significant ($p = 1.44 \times 10^{-6}$, $\beta = 0.49$) with the G allele decreasing the risk of hypertension (**FIG. 13**). rs2350620 is located in the intron 14 of *ASPH* (**FIG. 4B**). rs6770663 (A>G, MAF 0.08-0.09) is the next most statistically significant ($p = 4.79 \times 10^{-6}$, $\beta = 0.57$) with the G allele increasing the risk of hypertension (**FIG. 13**). rs6770663 is located in the intron 1 of *KCNAB1* (**FIG. 4C**). Among these ten variants, the only two with p -value < 0.05 in three out of the four studies were rs2350620 and rs6770663 (**Table 5**). **FIG. 13** shows the cumulative incidence of grade ≥ 2 hypertension for rs2350620 and rs6770663. For the SNP-based analysis of grade ≥ 3 , the Manhattan and Q-Q plots are shown in **FIG. 5**. 106 variants were identified as associated with hypertension (**Table 11**).

[0138] Forty-seven out of 106 variants had the same direction of effect (either reduced or increased risk) in at least three out of the four studies (cutoff $p < 1 \times 10^{-4}$). The top ten most statistically significant variants of that list are shown in **Table 7**. rs4782946 (G>A, MAF 0.37-0.43) was the most statistically significant ($p = 3.09 \times 10^{-7}$, $\beta = 0.66$) with the A allele increasing the risk of hypertension. rs4782946 is an intronic variant in *ATP2C2* (**FIG. 6**). rs17439529 (G>A, MAF 0.36-0.40) was the next most statistically significant ($p = 2.08 \times 10^{-6}$, $\beta = -0.72$) with the A allele decreasing the risk of hypertension. rs17439529 is located in the intron of *AKAP6* (**FIG. 6**).

Table 11. SNPs associated with hypertension (grade ≥ 3)

SNP	CH	BP	effect allele	reference allele	MAF 80303	MAF 40503	MAF 90401	MAF 40502	gene	feature	Flanking gene	Flanking gene	p-value	effect (β)
rs4782946	16	82979663	A	G	0.37	0.38	0.37	0.43	ATP2C2	intron	WFDIC1	KIAA1609	3.09E-07	0.66
rs3858416	11	100230559	A	G	.	0.06	.	0.05	FLJ32810	intron	LOC100128386	LOC100129602	7.29E-07	1.06
rs6807110	3	120338347	C	A	.	.	0.06	.	IGSF11	intron	LOC728873	C3orf30	1.27E-06	1.70
rs17439529	14	32253709	A	G	0.36	0.40	0.38	0.40	AKAP6	intron	MTCO1P2	NPAS3	2.08E-06	-0.72
rs10129969	14	77017051	G	A	.	0.06	.	0.09	THSD3	intron	AHSA1	SPTLC2	3.47E-06	1.04
rs9933396	16	78434745	G	A	0.06	.	0.05	.	NA	NA	LOC440389	LOC729847	4.68E-06	1.44
rs1530837	15	40069082	G	A	0.23	0.19	0.18	0.17	PLA2G4E	intron	EHD4	PLA2G4D	4.87E-06	0.66
rs11863271	16	82980316	A	G	0.20	0.17	0.19	0.22	ATP2C2	intron	WFDIC1	KIAA1609	5.23E-06	0.63
rs1171065	13	35359822	C	A	0.19	0.26	0.19	0.21	DCLK1	intron	NBEA	SOHLH2	5.73E-06	0.62
rs8010861	14	77018319	G	A	.	0.07	.	0.09	THSD3	intron	AHSA1	SPTLC2	5.92E-06	1.01
rs670362	18	10056414	A	G	0.18	0.14	0.11	0.12	NA	NA	VAPA	APCDD1	6.10E-06	0.67
rs17649232	2	182712983	G	A	0.07	.	0.06	.	NA	NA	PPP1R1C	PDE1A	7.08E-06	1.60
rs2665917	8	141032458	A	G	0.44	0.48	0.47	0.47	NIBP	intron	C8orf17	LOC100131910	7.13E-06	0.63
rs1048147	14	77209741	A	C	.	0.18	.	0.18	ALKBH1	utr-3	SPTLC2	RPL21P10	7.63E-06	0.78
rs11624101	14	77207812	A	G	.	0.18	.	0.18	ALKBH1	near-gene-3	SPTLC2	ALKBH1	7.63E-06	0.78
rs176955	14	77250973	G	A	.	0.18	.	0.18	C14orf156	intron	ALKBH1	SNW1	7.63E-06	0.78
rs10967306	9	2630805	A	G	0.07	0.07	0.09	0.08	VLDLR	intron	FLJ35024	KCNV2	8.16E-06	0.87
rs17091403	10	115923895	A	G	0.13	.	0.10	.	C10orf118	utr-5	ADRB1	TDRD1	9.41E-06	1.17
rs732121	13	95897355	G	A	0.06	.	0.07	.	H56ST3	intron	UGCG12	HSP90A86P	9.44E-06	1.35
rs12887282	14	77270338	C	A	.	0.18	.	0.18	SNW1	intron	C14orf156	C14orf178	9.68E-06	0.77
rs1320881	8	23934297	A	G	0.24	0.18	0.21	0.24	NA	NA	LOC100132107	ADAM28	9.86E-06	0.61
rs10011590	4	124693385	G	A	.	0.16	.	0.17	NA	NA	SPRY1	LOC644624	1.00E-05	0.77
rs4691370	4	157809201	G	A	0.06	0.09	.	0.07	NA	NA	hCG_1814936	PDGFC	1.00E-05	0.82
rs1008988	14	77330548	A	G	.	0.18	.	0.18	NA	NA	C14orf178	ADCK1	1.06E-05	0.77
rs11852645	15	68821216	C	A	.	0.13	.	0.09	UACA	intron	TLE3	LOC729611	1.08E-05	0.93

rs4632066	14	77317035	A	G	.	0.18	.	0.17	0.16	NA	NA	C14orf178	ADCK1	1.09E-05	0.77
rs10073306	5	58097612	A	G	0.19	0.18	0.17	0.16	0.16	RAB3C	intron	GAPT	PDE4D	1.12E-05	0.64
rs8088993	18	10052583	G	A	.	0.10	.	0.10	0.10	NA	NA	VAPA	APCDD1	1.26E-05	0.84
rs3821004	2	178188309	A	G	0.09	0.10	0.08	0.08	0.08	TTC30A	utr-3	TTC30B	PDE11A	1.31E-05	0.83
rs2505083	10	30375128	G	A	.	0.40	.	.	.	KIAA1462	intron	SVIL	LOC729663	1.33E-05	1.27
rs196584	7	36284221	A	G	0.07	0.13	0.09	0.07	0.07	EEPD1	intron	LOC100131181	KIAA0895	1.37E-05	0.75
rs10867852	9	84353502	A	G	0.08	0.07	0.06	0.06	0.06	NA	NA	LOC442427	RASEF	1.54E-05	1.01
rs1944142	11	130222650	G	A	.	0.45	.	.	0.49	NA	NA	C11orf44	SNX19	1.54E-05	0.72
rs7765461	6	1657305	C	A	.	0.20	.	.	0.15	GMD5	intron	FLJ46552	LOC100128372	1.68E-05	0.78
rs17749328	3	5538371	A	G	0.12	0.15	0.09	0.12	0.12	NA	NA	MRPS35P1	MRPS36P1	1.72E-05	0.70
rs10051270	5	58106740	A	C	0.14	0.17	0.14	0.13	0.13	RAB3C	intron	GAPT	PDE4D	1.76E-05	0.67
rs464349	16	88183752	A	G	0.45	0.47	0.50	0.48	0.48	CPNE7	intron	RPL13	DPEP1	1.86E-05	0.58
rs2858536	22	48127214	G	A	.	0.20	.	.	0.19	NA	NA	LOC643653	FLJ44385	2.04E-05	0.75
rs17078062	6	116992250	C	A	0.19	0.16	0.19	0.19	0.19	NA	NA	FAM26D	RWDD1	2.09E-05	0.64
rs7267054	20	17569201	A	G	0.08	.	0.08	.	.	RRBP1	intron	DSTN	BANF2	2.10E-05	1.30
rs7174784	15	99119567	G	A	.	.	0.41	.	.	NA	NA	ASB7	LOC440313	2.27E-05	1.42
rs2288502	5	156582630	A	G	0.07	0.07	0.06	0.06	0.06	ITK	intron	FAM718	CYFIP2	2.47E-05	0.89
rs540509	7	17071448	G	A	.	0.19	.	0.23	0.23	NA	NA	LOC100131425	LOC100131512	2.64E-05	0.73
rs8084568	18	57190720	A	G	0.08	0.12	0.09	0.09	0.09	NA	NA	hCG_1659830	LOC100129867	2.66E-05	0.77
rs4425091	2	165199471	G	A	.	0.26	.	.	0.29	NA	NA	GRB14	COBLL1	2.77E-05	0.70
rs11129096	3	2330167	A	G	.	0.30	0.33	0.34	0.34	CNTN4	intron	LOC727810	LOC100130346	2.99E-05	-0.75
rs7574859	2	29947713	C	A	0.11	0.15	0.17	0.21	0.21	ALK	intron	CLIP4	YPEL5	3.06E-05	0.60
rs35969878	2	226443471	G	A	.	0.09	.	.	0.11	NA	NA	KIAA1486	LOC646736	3.13E-05	0.88
rs2879464	3	182528567	G	A	.	0.45	.	.	0.42	NA	NA	DNAJC19	SOX2OT	3.21E-05	0.68
rs10206343	2	46019476	G	A	0.13	0.12	0.14	0.12	0.12	PRKCE	intron	SRBD1	EPAS1	3.50E-05	0.70
rs511092	15	27520966	G	A	0.32	0.34	0.34	0.35	0.35	NA	NA	NDNL2	LOC100130736	3.54E-05	0.55
rs6494889	15	68781337	A	G	.	0.13	.	.	0.09	UACA	intron	TLE3	LOC729611	3.68E-05	0.89
rs760628	22	27789732	G	A	0.22	0.22	0.24	.	.	NA	NA	C22orf31	KREMEN1	3.71E-05	0.73
rs2267760	14	77217446	A	G	.	0.19	.	0.20	0.20	ALKBH1	intron	SPTLC2	RPL21P10	3.76E-05	0.69

rs2323230	8	141012685	G	A		0.45	0.48	0.47	0.48	N/BP	intron	KCNK9	LOC100131910	3.78E-05	0.58
rs4320922	11	104627661	A	G			0.49		0.46	NA	NA	OR2AL1P	GRIA4	3.85E-05	-0.72
rs752280	2	174261681	C	A		0.13	0.11	0.14	0.11	NA	NA	LOC100129456	LOC644056	4.04E-05	0.73
rs1990236	17	11806187	A	G		0.20	0.18	0.19	0.18	DNAH9	missense	FLJ45455	ZNF18	4.11E-05	0.59
rs13062101	3	23458540	A	G		0.40	0.40	0.43	0.45	UBE2E2	intron	LOC100130785	UBE2E1	4.17E-05	0.53
rs11206344	1	54625582	C	A			0.44			SSBP3	intron	C1orf191	LOC645436	4.18E-05	-1.19
rs6463224	7	1106944	A	C		0.19			0.21	C7orf50	intron	GPB	ZFAND2A	4.18E-05	0.75
rs16954699	15	68789686	G	A			0.13		0.09	UACA	intron	TLE3	LOC729611	4.32E-05	0.88
rs2059322	15	68792114	C	A			0.13		0.09	UACA	intron	TLE3	LOC729611	4.32E-05	0.88
rs7075347	10	76203313	A	G		0.07		0.08		NA	NA	LOC645646	MYST4	4.36E-05	1.10
rs10988111	9	130559781	G	A		0.45		0.46		ZER1	intron	ZDHHC12	TBC1D13	4.39E-05	-1.09
rs1364075	16	85631051	C	A		0.30	0.33	0.32	0.34	NA	NA	LOC729979	LOC730018	4.39E-05	0.52
rs11855184	15	49594756	A	C			0.14		0.15	DMXL2	intron	GIDN	SCG3	4.48E-05	0.76
rs16933415	8	68660493	G	A					0.11	CPA6	intron	LOC100132812	PREX2	4.50E-05	1.02
rs1449047	11	104720707	A	G			0.15		0.16	NA	NA	OR2AL1P	GRIA4	4.52E-05	0.79
rs1514035	15	31357207	G	A		0.11	0.08	0.06	0.08	NA	NA	FMN1	RVR3	4.64E-05	0.81
rs9584088	13	92633700	A	C			0.20		0.20	NA	NA	GPC5	GPC6	4.88E-05	0.71
rs2585348	14	48194882	A	G		0.34	0.44	0.44	0.41	NA	NA	RPL18P1	ATP5GP2	4.92E-05	0.54
rs17708487	6	90700670	G	A		0.23	0.22	0.25	0.22	BACH2	intron	GIA10	LOC100129711	5.03E-05	0.56
rs7173605	15	21400911	G	A			0.11		0.13	NA	NA	MKRN3	MAGEL2	5.15E-05	0.83
rs11673509	19	5031647	A	G		0.09		0.08		JMID2B	intron	UHRF1	LOC100128439	5.26E-05	1.12
rs1078097	15	68795974	A	G			0.12		0.09	UACA	intron	TLE3	LOC729611	5.32E-05	0.87
rs406992	5	58117438	A	G		0.17	0.20	0.18	0.17	RAB3C	intron	GAPT	PDE4D	5.54E-05	0.61
rs6650294	13	102681443	G	A			0.10		0.10	NA	NA	SLC10A2	LOC728183	6.04E-05	0.79
rs10852800	17	11825241	A	G		0.20	0.18	0.19	0.18	ZNF18	intron	DNAH9	MAP2K4	6.18E-05	0.58
rs6598035	11	335595	A	G		0.35	0.37	0.29	0.31	NA	NA	IFITM3	B4GALNT4	6.23E-05	-0.62
rs6554770	5	13323090	A	G			0.17	0.17	0.14	NA	NA	CTNND2	LOC391738	6.28E-05	0.66
rs1011236	15	68818494	A	G			0.13		0.09	UACA	intron	TLE3	LOC729611	6.30E-05	0.88
rs12449769	17	11809087	G	A		0.21	0.18	0.19	0.19	DNAH9	intron	FLJ45455	ZNF18	6.34E-05	0.56

rs6778227	3	182516536	G	A	0.44	0.46	0.42	0.43	NA	NA	DNAJC19	SOX2OT	6.36E-05	0.53
rs293473	2	178196274	A	G	0.07	0.08	.	0.06	PDE11A	utr-3	TTC30A	LOC100131480	6.59E-05	0.87
rs723079	11	112699658	C	A	0.15	0.12	0.12	0.11	TTC12	intron	NCAM1	ANKK1	6.62E-05	0.62
rs966697	9	111119949	A	G	0.39	0.37	0.35	0.36	EPB41L4B	intron	C9orf4	PTPN3	6.69E-05	-0.60
rs11221807	11	129067604	G	A	.	0.16	.	0.16	NA	NA	BARX2	LOC729717	6.74E-05	0.74
rs1978368	2	205209582	A	C	0.09	.	0.08	.	PAR3B	intron	LOC100132669	NRP2	6.78E-05	1.12
rs17365340	5	113989891	A	C	0.10	0.09	0.06	0.09	NA	NA	KCNN2	TRIM36	6.84E-05	0.76
rs16954789	15	68823323	C	A	.	0.13	0.10	0.09	UACA	intron	TLE3	LOC729611	6.91E-05	0.83
rs1292299	18	10055917	G	A	0.21	0.15	0.15	0.15	NA	NA	VAPA	APCDD1	6.99E-05	0.57
rs10415904	19	9175135	C	A	0.14	0.16	0.18	0.15	NA	NA	OR7E16P	OR7E25P	7.00E-05	0.59
rs2386717	16	72370567	A	C	0.32	.	0.30	.	NA	NA	C16orf47	LOC441506	7.03E-05	0.89
rs7328957	13	103355842	G	A	0.12	0.11	0.11	0.13	NA	NA	LOC728183	DAOA	7.27E-05	0.69
rs13374607	1	182693445	G	A	0.08	.	0.07	0.07	C1orf21	intron	TSEN15	LOC100129573	7.57E-05	0.93
rs16924767	12	22260834	G	A	0.13	.	0.16	.	ST8SIA1	intron	CMAS	KIAA0528	7.58E-05	1.17
rs17543819	5	89989605	A	G	0.06	.	0.08	.	GPR98	synonymous	LYSMD3	LOC729040	7.77E-05	1.12
rs17344132	13	103339702	G	A	0.10	0.11	0.09	0.11	NA	NA	LOC728183	DAOA	7.85E-05	0.67
rs2503697	13	72567440	A	G	.	0.06	.	0.06	NA	NA	KLF5	FABP5L1	8.96E-05	0.90
rs17622455	5	90031559	G	A	0.06	.	0.08	.	GPR98	intron	LYSMD3	LOC729040	9.33E-05	1.11
rs7717673	5	135239365	A	G	0.11	0.12	0.12	0.11	NA	NA	LOC153328	IL9	9.37E-05	0.68
rs4519437	18	63045205	A	G	.	0.10	.	0.08	NA	NA	CDH19	DSEL	9.42E-05	0.83
rs1213236	11	84849951	A	G	0.07	.	.	0.07	NA	NA	DIG2	TMEM126B	9.49E-05	0.94
rs17019472	2	36780787	G	A	0.13	0.11	0.14	0.14	VIT	intron	FEZ2	STRN	9.93E-05	0.6266
rs4506930	16	75154359	G	A	0.40	.	0.41	.	NA	NA	CNTNAP4	LOC100128497	9.93E-05	-1.0612

[0139] For the gene-based analysis of grade ≥ 2 , the Q-Q plot is shown in FIG. 7. Table 9 shows the ten most statistically significant genes. *UNC50* was the most statistically significant gene ($p=2.30 \times 10^{-5}$).

Variants and genes associated with bevacizumab-induced proteinuria and hypertension (composite toxicity)

[0140] For the SNP-based analysis of grade ≥ 2 , the Manhattan and Q-Q plots are shown in FIG. 2. 100 variants associated with composite toxicity were identified (Table 12).

Table 12. SNPs associated with composite toxicity (grade ≥ 2)

SNP	CH BP	effect allele	reference allele	MAF 80303	MAF 40503	MAF 90401	gene	feature	Flanking gene	Flanking gene	p-value unadjusted	effect (β) unadjusted	p-value adjusted	effect (β) adjusted
rs17084411	6 1226 9267 9	A	G	.	0.11	.	NA	NA	LOC644502	HSF2	4.24E-08	1.52	4.74E-08	1.55
rs1927869	6 1226 2741 9	T	C	.	0.11	.	NA	NA	LOC644502	HSF2	4.24E-08	1.52	4.74E-08	1.55
rs17084371	6 1226 1211 1	G	A	.	0.11	.	NA	NA	LOC644502	HSF2	7.24E-08	1.47	8.05E-08	1.49
rs11036390	1 4138 7322 1	C	A	.	0.27	.	NA	NA	LRR4C	LOC100131020	2.15E-07	1.02	2.37E-07	1.02
rs11662763	1 5847 8091	A	G	0.14	0.11	0.13	NA	NA	LOC645355	TTMA	9.19E-07	0.67	9.48E-05	0.61
rs2937754	5 1730 8803	G	A	.	0.19	.	BASP1	intron	FLJ34047	LOC646012	1.52E-06	0.95	1.52E-06	0.97
rs8006648	1 8735 4 9052	A	G	0.27	0.28	0.26	NA	NA	LOC730121	GALC	2.33E-06	0.58	2.87E-05	0.55
rs2456761	1 6220 0 0548	A	C	0.35	.	0.34	NA	NA	LOC729184	CDC2	2.80E-06	0.72	4.57E-05	0.69
rs1000032	2 1766 4377 1	A	C	0.13	0.18	0.19	NA	NA	KIAA1715	EVX2	3.21E-06	0.62	9.26E-06	0.63
rs2203208	1 5725 2 7435	G	A	.	0.20	.	NA	NA	LOC100127973	LRI3	3.54E-06	0.96	3.05E-06	1.00
rs2687640	7 2913 8781	A	G	0.06	.	0.06	CPVL	intron	KIAA0644	LOC100131724	3.55E-06	1.03	1.09E-06	1.13

rs931 0707	3	2307 104	A	G	0.37	0.37	0.36	CNTN4	intron	LOC727 810	LOC100 130346	4.03E-06	0.53	1.33E-05	0.52
rs719 7696	1 6	6110 274	G	A	.	0.14	.	A2BP1	intron	LOC100 129334	LOC440 337	5.95E-06	1.15	6.41E-06	1.16
rs999 1738	4	1823 4104		T	.	0.49	.	NA	NA	hCG_20 25798	LOC132 386	7.26E-06	0.84	5.79E-06	0.86
rs125 97709	1 6	6102 147	G	A	.	0.13	.	A2BP1	intron	LOC100 129334	LOC440 337	7.29E-06	1.14	7.36E-06	1.14
rs131 56044	5	1392 0851	A	G	0.15	0.11	0.11	DNAH5	intron	LOC391 738	TRIO	8.51E-06	0.60	7.40E-05	0.59
rs123 28055	2	4982 4743	A	G	0.06	.	0.05	NA	NA	FSHR	LOC130 728	9.19E-06	0.99	2.27E-03	0.76
rs479 9369	1 8	3059 4128	G	A	0.20	0.20	0.18	DTNA	intron	LOC646 842	MAPRE 2	1.14E-05	0.59	1.63E-03	0.44
rs116 10946	1 2	3985 117	G	A	.	0.14	.	NA	NA	PARP11	LOC399 988	1.19E-05	0.96	1.21E-05	0.96
rs750 585	5	1686 4489			.	0.13	.	SLIT3	intron	LOC728 095	CCDC99	1.24E-05	1.03	1.30E-05	1.04
rs275 7491	1	1705 3342	A	G	0.06	.	0.06	DNM3	intron	LOC100 128178	LOC100 131486	1.25E-05	0.90	1.39E-02	-0.68
rs275 7500	1	1705 4564	A	G	0.06	.	0.06	DNM3	intron	LOC100 128178	LOC100 131486	1.25E-05	0.90	1.39E-02	0.28
rs177 52325	4	6592 7951	A	G	0.11	.	0.13	EPHA5	intron	LOC644 682	LOC642 828	1.38E-05	0.77	1.05E-05	0.82
rs720 4266	1 6	9876 004	G	A	0.28	.	0.28	GRIN2A	intron	LOC653 737	LOC727 844	1.44E-05	0.60	6.84E-06	0.69
rs127 54186	1	1963 8913	T	G	.	0.11	.	CAPZB	intron	LOC100 130193	C1orf15 1	1.65E-05	0.98	1.14E-05	0.99

rs720 2526	1 6	6808 380	A	G		0.30	0.30	0.29	A2BP1	intron	LOC100 131413	LOC100 131080	1.67E-05	0.51	2.35E-05	0.52
rs100 1952	1 1	4142 1246	C	T	.	0.26	0.26	.	NA	NA	LRRC4C	LOC100 131020	1.74E-05	0.87	1.74E-05	0.87
rs111 54658	6 2	1324 2225	G	T	.	0.13	0.13	.	LOC100 131774	intron	CTGF	MOXD1	1.75E-05	0.98	1.51E-05	0.99
rs755 3399	1 3	3406 309	C	A	.	0.25	0.25	.	MEGF6	misse nse	ARHGEF 16	TPRG1L	1.81E-05	0.95	1.46E-05	0.91
rs135 8206	3 4	7419 8360	G	A	0.30	. 0.10	0.30	0.31	NA	NA	LOC100 129282	HSP90A B5P	1.81E-05	0.62	3.89E-03	0.45
rs178 67545		1188 7313	T	C	.	0.10	0.10	.	NA	NA	NT5C3P 1	NDST3	1.84E-05	1.20	1.57E-05	1.23
rs169 45809	1 7	1241 236	G	A	0.08	0.08	0.08	0.06	YWHAЕ	intron	TUSC5	LOC727 845	2.00E-05	0.80	2.16E-06	0.94
rs723 4672	1 8	5875 157	A	G	0.15	.	0.15	0.14	NA	NA	LOC645 355	TTMA	2.06E-05	0.72	1.03E-03	0.64
rs130 62101	3 	2345 8540	A	G	0.40	0.40	0.40	0.43	UBE2E2	intron	LOC100 130785	UBE2E1	2.34E-05	0.45	4.35E-05	0.46
rs108 20743	9 	1067 1148	G	A	0.29	0.28	0.29	0.27	ABCA1	intron	NIPSNА P3В	SLC44A 1	2.42E-05	0.48	8.05E-05	0.47
rs720 1930	1 6	9866 156	G	A	0.29	.	0.29	0.33	GRIN2A	intron	LOC653 737	LOC727 844	2.90E-05	0.60	4.51E-05	0.65
rs127 06180	7 	1177 8494	A	G	0.34	.	0.34	.	NA	NA	ANKRD 7	LOC648 442	3.03E-05	0.91	8.37E-04	0.97
rs993 3832	1 6	9856 135	A	G	0.29	.	0.29	0.32	GRIN2A	intron	LOC653 737	LOC727 844	3.24E-05	0.59	5.18E-05	0.64
rs670 6281	2 3	1901 6099	C	A	.	0.26	0.26	.	NA	NA	SLC40A 1	ASNSD1	3.27E-05	0.91	2.54E-05	0.94

rs143 7883	2	1901 6771 3	C	T	.	0.25	.	NA	NA	SLC40A 1	ASNSD1	3.35E-05	0.90	2.81E-05	0.93
rs440 7684	6	8550 0368	A	G	0.47	.	0.53	TBX18	near- gene- 3	LOC442 233	TBX18	3.48E-05	0.59	1.40E-03	0.49
rs414 9265	9	1067 1231 9	A	G	0.29	0.28	0.27	ABCA1	intron	NIPSN P3B	SLC44A 1	3.57E-05	0.47	1.20E-04	0.46
rs172 02944	8	1384 8320	G	T	.	0.33	.	NA	NA	C8orf48	SGCZ	3.70E-05	-0.82	2.53E-05	-0.85
rs473 8274	8	5664 5881	A	C	0.29	.	0.27	NA	NA	XKR4	TMEM6 8	3.72E-05	0.60	3.16E-03	0.49
rs277 311	5	1544 7398 3	A	G	0.14	0.14	0.14	NA	NA	LOC100 131520	LOC100 130088	3.88E-05	0.62	3.47E-04	0.60
rs286 6223	4	1017 4497 1	G	A	0.19	0.18	0.21	NA	NA	EMCN	LOC728 771	3.96E-05	0.56	2.40E-03	0.43
rs761 4155	3	7419 6658	G	A	0.25	.	0.27	NA	NA	LOC100 129282	HSP90A B5P	4.05E-05	0.61	8.67E-03	0.42
rs696 6727	7	1300 2535 4	G	A	0.06	.	.	NA	NA	TSGA13	KLF14	4.07E-05	1.31	1.26E-01	0.78
rs698 2610	8	1455 7840	C	A	.	0.36	.	SGCZ	intron	LOC100 131565	TUSC3	4.39E-05	0.77	3.36E-05	0.78
rs924 945	1 8	6758 6419	A	G	0.34	0.41	0.34	NA	NA	LOC100 132647	CBLN2	4.48E-05	0.46	3.54E-05	0.49
rs170 21160	2	3771 7573	T	G	.	0.07	.	NA	NA	QPCT	CDC42E P3	4.52E-05	1.29	4.99E-05	1.30
rs992 1541	1 6	9899 263	A	C	0.23	.	0.24	GRIN2A	intron	LOC653 737	LOC727 844	4.52E-05	0.59	5.20E-05	0.64

rs225 0378	1	7391	C	T	.	0.23	.	LOC100 130268	near- gene- 5	KCNC2	LOC100 130268	4.63E-05	0.88	4.85E-05	0.89
rs351 572	8	1606	G	A	0.40	0.49	0.44	MSR1	intron	hCG_17 94003	LOC646 440	4.81E-05	-0.46	1.43E-04	-0.45
rs116 42239	1	9904	G	A	0.25	0.28	0.25	GRIN2A	intron	LOC653 737	LOC727 844	4.83E-05	0.48	1.14E-04	0.49
rs148 0802	8	1362	C	A	0.37	.	0.38	NA	NA	ZFAT	LOC286 094	4.97E-05	0.63	2.50E-05	0.70
rs288 6725	5	3780	A	G	.	0.14	.	NA	NA	WDR70	GDNF	4.99E-05	0.97	4.89E-05	1.02
rs152 4145	2	3597	T	G	.	0.43	.	NA	NA	MRPL5 OP1	CRIM1	5.01E-05	0.84	5.05E-05	0.84
rs125 25751	6	1094	A	G	0.24	0.19	0.22	SESN1	intron	ARMC2	C6orf18 2	5.04E-05	0.51	1.31E-03	0.43
rs207 7923	1	9788	G	A	0.29	.	0.32	GRIN2A	intron	LOC653 737	LOC727 844	5.21E-05	0.59	1.20E-04	0.61
rs785 3963	9	8290	A	G	0.15	.	0.14	NA	NA	LOC100 128222	TLE1	5.21E-05	0.72	5.12E-03	0.56
rs141 0171	6	8545	A	G	0.47	.	0.53	NA	NA	LOC442 233	TBX18	5.23E-05	0.57	2.18E-03	0.47
rs190 4982	1	1050	T	C	.	0.50	.	NA	NA	LOC642 337	LOC100 130867	5.24E-05	-0.75	3.54E-05	-0.80
rs127 06181	7	1177	A	G	0.34	.	.	NA	NA	ANKRD 7	LOC648 442	5.28E-05	0.88	1.09E-03	0.95
rs134 5697	5	1479	G	A	0.48	0.49	0.51	HTR4	intron	FBXO38	ADRB2	5.49E-05	-0.46	6.06E-04	-0.41

rs112 55686	1 0	8496 013	C	A	.	0.46	.	NA	NA	LOC389 935	KRT8P1 6	5.56E-05	0.80	5.51E-05	0.81
rs181 4343	1 1	1290 7046		G	0.23	0.23	0.26	NA	NA	BARX2	LOC729 717			1.32E-03	0.42
rs772 4465	5	4723 864	A	G	.	0.06	.	NA	NA	IRX1	LOC340 094	5.92E-05	1.11	4.19E-05	1.15
rs132 58175	8	1387 3685	A	G	.	0.45	.	NA	NA	C8orf48	SGCZ	5.97E-05	0.72	3.14E-05	0.77
rs782 1773	8	9748 866	G	A	0.08	0.05	0.08	NA	NA	TNKS	MSRA	5.98E-05	0.71	1.75E-05	0.80
rs156 4470	8	1362 9011			0.30	.	0.32	NA	NA	ZFAT	LOC286 094				
rs676 3279	3	7419 5448	G	A	0.25	0.29	0.27	NA	NA	LOC100 129282	HSP90A B5P	6.28E-05	0.46	5.01E-03	0.34
rs224 3628	1 0	7553 828	A	G	0.37	.	0.34	NA	NA	LOC728 777	ITI15	6.39E-05	0.53	1.87E-03	0.46
rs107 92038	1	5607 9983	G	A	0.34	.	0.38	NA	NA	OR5M1 1	OR5M1 0	6.59E-05	0.61	1.81E-05	0.72
rs130 24296	2	2242 9874			0.17	.	0.20	NA	NA	LOC646 696	AP1S3				
rs796 8026	1 2	8375 4187	A	G	0.31	.	0.30	NA	NA	LOC100 128335	SLC6A1 5	6.89E-05	0.57	3.63E-05	0.64
rs419 58	7	1177 6068		G	0.35	.		NA	NA	ANKRD 7	LOC648 442	7.07E-05	0.87	1.26E-03	0.94
rs254 3540	1 7	7572 396	A	G	.	0.40	.	DNAH2	intron	EFNB3	RPL29P 2	7.09E-05	-0.77	7.26E-05	-0.77
rs176 15862	1 4	4393 1394	T	C	.	0.25	.	NA	NA	YWHAZ P1	LOC729 165	7.21E-05	0.86	7.33E-05	0.86

rs693	1	5604	A	G		0.34	.	0.38	NA	NA	OR5M6 P	OR5M5 P	7.58E-05	0.60	2.16E-05	0.71
996	1	6568	A													
rs112	2	1901							SLC40A 1	intron	WDR75	ASNSD1				
3110		5244 4	C	T		. 0.34							7.70E-05	0.72	7.56E-05	0.72
rs775	6	1324							LOC100 131774	intron	CTGF	MOXD1				
4913		2354 8	C	A		0.11	0.13	0.13					8.10E-05	0.58	1.07E-04	0.60
rs986	3	1777							NA	NA	LOC730 168	TBL1XR 1				
rs361		6936 2	G	A		.		0.03					8.36E-05	1.63	9.80E-05	1.62
rs294	4	2295							LOC643 751	intron	G8A3	PPARGC 1A				
0774		8441	A	G		0.17	.	0.25					8.60E-05	0.62	9.16E-04	0.58
rs121	1	1083							NA	NA	VAV3	SLC25A 24				
9769		4014 9	A	G		0.32	.	0.32					8.65E-05	0.62	6.64E-03	0.47
rs297	8	7123							NCOA2	intron	H2AFZP 2	BTF3L2	8.76E-05	1.31	2.62E-03	1.36
7983		3342	A	G		0.06	.									
rs483	8	1387							NA	NA	C8orf48	SGCZ	8.93E-05	-0.72	6.57E-05	-0.74
1257		8742	A	G		.	0.40	.								
rs804	1	7401							A2BP1	intron	LOC100 131413	LOC100 131080	9.07E-05	-0.68	6.74E-04	-0.62
9793	6	978	C	A		0.19	0.17	0.17								
rs772	5	6825							NA	NA	PIK3R1	LOC100 130639	9.11E-05	0.82	9.54E-05	0.82
5683		5470	G	A		.	0.23	.								
rs220	1	1849							PTGS2	utr-3	LOC100 131939	PLA2G4 A				
6593		0905 2	A	G		0.08	.						9.14E-05	1.30	3.03E-04	1.49
rs703	9	9193							NA	NA	IL6RL1	OR7E31 P	9.17E-05	0.68	4.55E-06	0.85
8808		1116	A	G		0.13	.	0.15								
rs809	1	6766							NA	NA	LOC100 132647	CBLN2				
8087	8	2582	A	G		0.23	0.28	0.22					9.23E-05	0.47	1.62E-04	0.49
rs172	3	4118				0.45	0.50	0.52	NA	NA	RPS27P 4	MRPS3 1P1				
52114		7757	A	G									9.33E-05	-0.43	6.44E-04	-0.40

rs980 5752	1 3	1138 9453 1	A	G	.	.	0.16	RASA3	intron	FAM70 B	CDC16	9.44E-05	0.86	4.96E-05	0.90
rs122 72563	1 1	3246 5808	A	G	.	0.20	.	NA	NA	WIT1	EIF3M	9.46E-05	0.85	8.00E-05	0.86
rs222 151	2 1	2669 2482	A	G	0.25	0.23	0.22	NA	NA	APP	CYR1	9.49E-05	-0.57	9.10E-06	-0.73
rs873 930	1 0	7569 980	G	A	0.46	0.47	0.43	NA	NA	LOC728 777	ITIH5	9.58E-05	0.40	4.49E-04	0.39
rs105 02634	1 8	3057 0172	G	A	0.11	0.09	0.10	DTNA	intron	LOC646 842	MAPRE 2	9.58E-05	0.67	1.56E-03	0.57
rs134 9498	2	1733 0085 2	A	G	0.17	0.22	0.19	NA	NA	LOC100 129169	RAPGEF 4	9.73E-05	0.50	1.51E-03	0.45
rs270 4783	2	1462 1642 9	C	T	.	0.28	.	NA	NA	LOC730 124	LOC727 713	9.84E-05	0.87	1.00E-04	0.87

[0141] Fifty-seven out of the 100 variants had the same direction of effect in at least two out of the three trials (cutoff $p < 1 \times 10^{-4}$). The top ten most statistically significant variants of that list are shown in **Table 5**. rs11662763 (G>A, MAF 0.11-0.14) was the most statistically significant ($p = 9.19 \times 10^{-7}$, $\beta = 0.67$), with the A allele increasing the risk of composite toxicity (**FIG. 3**). rs11662763 is 33 kb 3' from TTMA (**FIG. 4A**).

[0142] For the SNP-based analysis of grade ≥ 3 , the Manhattan and Q-Q plots are shown in **FIG. 5**. 88 variants were identified as associated with composite toxicity (**Table 13**). Fifty-three out of 88 variants had the same direction of effect (either reduced or increased risk) in at least three out of the four studies (cutoff $p < 1 \times 10^{-4}$). The top ten most statistically significant variants of that list are shown in **Table 7**. rs10867852 (G>A, MAF 0.06-0.08) was the most statistically significant ($p = 1.46 \times 10^{-6}$, $\beta = 1.16$), with the A allele increasing the risk of composite toxicity. rs10867852 is an intergenic variant located 430 kb 3' from RASEF (**FIG. 6**). rs7717673 (G>A, MAF 0.11-0.12) was the next most statistically significant ($p = 3.93 \times 10^{-6}$, $\beta = 0.94$) with the A allele increasing the risk of composite toxicity. rs7717673 is located in the intron of *SLC25A48* (**FIG. 6**).

Table 13. SNPs associated with composite toxicity (grade ≥ 3)

SNP	CH	BP	Effect allele	reference allele	MAF 80303	MAF 40503	MAF 90401	gene	feature	Flanking gene	Flanking gene	p-value	effect (β)
rs6807110	3	120338347	C	A	.	.	0.06	IGSF11	intron	LOC728873	C3orf30	1.29E-06	1.61
rs10867852	9	84353502	A	G	0.08	0.07	0.06	NA	NA	LOC442427	RASEF	1.46E-06	1.16
rs1022306	11	83629022	A	C	.	0.13	.	DLG2	intron	LOC100130985	LOC100130066	2.11E-06	1.32
rs6954042	7	109951683	G	A	.	0.06	.	NA	NA	LOC646620	IMMP2L	2.45E-06	1.76
rs7717673	5	135239365	A	G	0.11	0.12	0.12	SLC25A48	intron	LOC153328	IL9	3.93E-06	0.94
rs2478835	10	30357955	T	C	.	0.40	.	KIAA1462	synonymous	SVIL	LOC729663	8.85E-06	1.22
rs4842232	9	137279808	A	G	.	0.10	.	NA	NA	LOC401557	C9orf62	9.83E-06	1.55
rs4320922	11	104627661	A	G	.	0.49	.	NA	NA	OR2AL1P	GRIA4	1.27E-05	-1.24
rs6033941	20	14243645	C	A	.	0.29	.	MACROD2	intron	SCYE1P	FLRT3	1.40E-05	1.05
rs2454331	8	89957664	G	A	0.43	0.40	0.43	NA	NA	LOC100129100	RIPK2	1.43E-05	-0.77
rs873224	8	142600146	G	A	0.11	0.10	0.08	NA	NA	FLJ43860	LOC100131146	1.48E-05	0.86
rs10873360	14	25663831	T	G	.	0.11	.	NA	NA	LOC401767	NOVA1	1.49E-05	1.38
rs966439	14	86235074	G	A	0.21	0.17	0.16	NA	NA	LOC283584	LOC283585	1.52E-05	0.70
rs7849777	9	136812622	A	G	0.09	0.05	0.06	COL5A1	intron	RXRA	LOC100130622	1.56E-05	1.31
rs10869538	9	70729551	G	A	0.15	0.16	0.15	PIP5K1B	intron	LOC100131240	PRKACG	1.74E-05	0.74
rs11664759	18	69223208	A	G	0.11	0.15	0.15	NA	NA	LOC400655	FBXO15	2.21E-05	0.83
rs1978259	14	86265207	A	C	0.20	.	0.16	NA	NA	LOC283584	LOC283585	2.63E-05	0.81
rs7174784	15	99119567	G	A	.	.	0.41	NA	NA	ASB7	LOC440313	2.74E-05	1.25
rs17096208	14	73625022	A	G	0.08	.	0.07	LIN52	intron	ALDH6A1	V5X2	2.87E-05	1.05
rs4646864	14	73596456	A	G	0.08	.	0.07	ALDH6A1	near-gene-3	ENTPD5	ALDH6A1	2.87E-05	1.05
rs17109031	12	52884634	A	G	0.13	0.08	0.10	NA	NA	SMUG1	LOC100132010	2.93E-05	0.85
rs4696433	4	154307393	A	G	0.12	0.10	0.12	NA	NA	FHDC1	TRIM2	3.01E-05	0.90
rs6739406	2	35467180	A	G	0.11	0.13	0.09	NA	NA	LOC100130842	MRPL50P1	3.11E-05	0.84
rs10988111	9	130559781	G	A	0.45	.	0.46	ZER1	intron	ZDHHC12	TBC1D13	3.21E-05	-0.97
rs491451	6	12836804	A	G	0.16	0.11	0.14	PHACTR1	intron	RPL15P3	LOC100130357	3.45E-05	0.80

rs16930838	8	65151961	C	T	.	0.11	.	.	0.11	.	NA	NA	IFITM8P	LOC100130155	3.50E-05	1.31
rs2505083	10	30375128	C	T	.	0.40	.	.	0.40	.	KIAA1462	intron	SVIL	LOC729663	3.55E-05	1.11
rs10129969	14	77017051	G	A	.	0.06	.	.	0.06	.	THSD3	intron	AHSA1	SPTLC2	3.73E-05	1.54
rs1452243	12	83695187	A	C	0.38	0.34	0.39	NA	0.34	0.39	NA	NA	LOC100128335	SLC6A15	3.73E-05	0.68
rs11254929	10	7072177	G	A	0.16	.	0.17	NA	0.16	0.17	NA	NA	LOC439949	SFMBT2	3.91E-05	0.94
rs710392	5	87060900	T	C	.	0.17	.	NA	0.17	.	NA	NA	CCNH	TMEM161B	4.02E-05	1.20
rs1932065	1	70857226	G	A	.	0.23	.	NA	0.23	.	NA	NA	LOC391048	PTGER3	4.03E-05	1.02
rs12157031	0	NA	T	C	.	0.08	.	NA	0.08	.	NA	NA	RPS6KA3	CNKSR2	4.33E-05	1.52
rs7080002	10	109119252	G	A	.	0.06	.	NA	0.06	.	NA	NA	SORCS1	LOC100128304	4.38E-05	1.64
rs3739998	4	118873138	G	C	.	0.40	.	NA	0.40	.	NA	NA	NT5C3P1	NDST3	4.38E-05	1.06
rs17867545	14	61622536	T	C	.	0.10	.	SYT16	0.10	.	NA	intron	MOCS3P	LOC100128793	4.57E-05	1.43
rs2154110	6	2465335	G	T	.	0.25	.	NA	0.25	.	NA	NA	LOC100128372	C6orf195	4.68E-05	1.17
rs7764946	6	6613180	T	C	.	0.07	.	NA	0.07	.	NA	NA	LY86	RP11-320C15.1	5.05E-05	1.55
rs9405313	8	33984189	A	C	0.11	0.13	0.12	NA	0.13	0.12	NA	NA	CYCSP3	LOC137107	5.07E-05	0.80
rs4493901	6	22511446	T	C	.	0.11	.	NA	0.11	.	NA	NA	PRL	HDGFL1	5.10E-05	1.18
rs2655439	6	14056368	A	G	0.15	0.14	0.13	RNF182	0.14	0.13	NA	intron	CCDC90A	MRPL35P1	5.42E-05	0.75
rs1192057	14	88559840	A	G	.	0.10	.	NA	0.10	.	NA	NA	TTC8	LOC390501	5.55E-05	1.34
rs11628605	4	56789252	A	G	.	0.32	.	KIAA1211	0.32	.	NA	intron	CEP135	MRPL22P1	5.56E-05	1.11
rs17751450	9	25541627	A	G	0.36	.	0.38	NA	.	0.38	NA	NA	C9orf134	TUSC1	5.66E-05	0.75
rs7028018	20	40742146	G	A	0.29	0.38	.	PTPRT	0.38	.	NA	intron	LOC643172	PPIAL	5.76E-05	0.73
rs2206428	12	72205105	A	G	0.25	.	0.30	NA	.	0.30	NA	NA	TRHDE	LOC100128674	5.90E-05	0.81
rs12368298	10	76203313	G	A	0.19	.	.	NA	.	.	NA	NA	LOC645646	MYST4	6.03E-05	1.31
rs7075347	7	36284221	A	G	0.07	.	0.08	EEPD1	.	0.08	NA	intron	LOC100131181	KIAA0895	6.06E-05	1.01
rs196584	9	117317136	A	G	0.07	0.13	0.09	NA	0.13	0.09	NA	NA	43800	C9orf27	6.13E-05	0.76
rs9408872	20	14192971	A	C	.	0.22	.	MACROD2	0.22	.	NA	intron	SCYE1P	FLRT3	6.39E-05	1.06
rs1998238	11	104663936	A	G	.	0.29	.	NA	0.29	.	NA	NA	ORZAL1P	GRIA4	6.42E-05	0.99
rs10895805	5	39716478	A	G	.	0.41	.	NA	0.41	.	NA	NA	LOC100129040	LOC285634	6.42E-05	-1.28
rs10473145	1	25124011	T	G	.	0.15	.	RUNX3	0.15	.	NA	intron	CLIC4	LOC391020	6.68E-05	1.07
rs742230	9	70717983	C	T	.	0.43	.	PIP5K1B	0.43	.	NA	intron	LOC100131240	PRKACG	6.69E-05	-1.20

rs1414954	1	156145769	A	G	0.13	.	0.11	NA	NA	LOC649203	hCG_1994895	6.72E-05	0.85
rs4450009	12	74414178	G	A	0.16	0.13	0.13	NA	NA	LOC100130336	LOC100131830	6.72E-05	0.72
rs4831949	13	80958452	G	A	.	0.08	.	NA	NA	LOC100129023	PTMAP5	6.80E-05	1.48
rs9545728	20	40760195	A	G	0.19	.	.	PTPRT	intron	LOC643172	PPIAL	6.85E-05	1.38
rs6072833	9	116819754	A	G	0.25	.	0.30	NA	NA	TNFSF8	TNC	6.87E-05	0.80
rs1107373	5	92355984	A	G	0.06	0.08	0.09	NA	NA	CCTP2	LOC391811	7.14E-05	0.83
rs12054859	10	30346810	G	A	0.07	.	.	KIAA1462	utr-3	SVIL	LOC729663	7.28E-05	1.87
rs2478839	13	66879378	T	C	.	0.42	.	NA	NA	LOC400141	LOC390411	7.37E-05	1.03
rs13378216	6	143400706	G	T	.	0.06	.	NA	NA	HIVEP2	AIG1	7.41E-05	1.39
rs12664681	18	55864775	C	A	0.06	0.06	0.08	NA	NA	LOC728115	LOC400652	7.65E-05	0.93
rs17066548	13	95897355	A	C	0.05	.	0.05	HS6ST3	intron	UGCGL2	HSP90AB6P	7.74E-05	1.34
rs732121	20	40763167	G	A	0.06	.	0.07	PTPRT	intron	LOC643172	PPIAL	7.93E-05	1.12
rs3092743	1	29428986	A	G	0.17	.	0.20	MECR	intron	SFRS4	PTPRU	8.19E-05	0.79
rs2819606	2	174388565	T	C	.	0.10	.	NA	NA	LOC100129456	LOC644056	8.19E-05	1.37
rs16862115	5	168644898	A	G	0.20	0.21	0.24	SLIT3	intron	LOC728095	CCDC99	8.61E-05	0.60
rs750585	6	134606559	G	A	.	0.13	.	NA	NA	SGK1	LOC442261	8.66E-05	1.06
rs9493871	16	78430806	A	C	0.09	0.07	0.08	NA	NA	LOC440389	LOC729847	8.66E-05	0.96
rs11644568	6	1773164	A	C	0.06	.	0.05	GMDS	intron	FLI46552	LOC100128372	8.83E-05	1.18
rs93228072	2	50099333	G	A	0.28	0.26	0.31	NRXN1	intron	LOC130728	LOC730100	9.04E-05	0.63
rs7568888	4	109997382	A	G	.	.	0.15	COL25A1	intron	LOC100129714	ZCCHC23	9.10E-05	1.17
rs1377208	8	58380598	C	A	0.18	.	.	NA	NA	C8orf71	LOC100130588	9.11E-05	1.19
rs1878628	11	104715682	G	A	.	.	0.07	NA	NA	OR2AL1P	GRIA4	9.11E-05	1.35
rs4603276	11	104778916	G	A	.	0.41	.	NA	NA	OR2AL1P	GRIA4	9.13E-05	-1.22
rs7930393	8	24652844	C	T	.	0.41	.	NA	NA	ADAM7	NEFM	9.13E-05	-1.22
rs10091523	9	116740531	G	A	0.34	.	0.36	NA	NA	TNFSF8	TNC	9.31E-05	0.82
rs4979476	13	35359822	G	A	0.09	0.09	0.08	DCLK1	intron	NBEA	SOHLH2	9.33E-05	0.73
rs1171065	9	92388224	C	A	0.19	0.26	0.19	NA	NA	LOC340515	DIRAS2	9.34E-05	0.63
rs16906689	5	37808537	A	G	.	0.09	.	NA	NA	WDR70	GDNF	9.45E-05	1.43
rs10472291	7	3583940	A	C	.	0.37	.	SDK1	intron	LOC100129603	LOC730351	9.53E-05	1.04

rs9654994	17	67535422	G	A	0.14	0.15	0.15	NA	NA	hCG_1644301	FLJ37644	9.64E-05	0.76
rs12451606	1	61132767	G	A	.	.	0.03	NA	NA	C1orf87	NFIA	9.67E-05	1.83
rs1002005	8	24655238	G	A	0.06	0.08	0.07	NA	NA	ADAM7	NEFM	9.75E-05	0.83
rs4543550	10	93349774	G	A	0.34	.	0.36	NA	NA	HECTD2	PPP1R3C	9.92E-05	0.82
rs7903829	3	2307104	A	C	0.06	0.07	0.07	CNTN4	intron	LOC727810	LOC100130346	9.97E-05	0.90

[0143] For the gene-based analysis of grade ≥ 2 , the Q-Q plot is shown in FIG. 7. Table 9 shows the ten most statistically significant genes. SLC25A24 was the most significant ($p=4.00 \times 10^{-6}$).

Discussion

[0144] It is believed that this is the largest GWAS of bevacizumab-induced proteinuria and hypertension. The present study included 1,041 cancer patients, with different tumor types, from four randomized phase III clinical trials conducted at the Alliance. The relatively large sample size, the randomized design, and the standardized collection of the phenotypic and genotypic data are positive features that increase the value of these findings. The analysis of genetic associations that were consistent across different studies led to the identification of novel SNPs and genes associated with these toxicities.

[0145] This study has selected *DNAH5*, *TRIO*, *RIPK4* and IL17F as genes involved bevacizumab-induced proteinuria. *DNAH5* and *TRIO* are the closest genes from rs339947, the most statistically significant SNP associated with proteinuria ($p=7.66 \times 10^{-8}$). *DNAH5* encodes a dynein protein (part of a microtubule-associated motor protein complex) that is important for the normal function of ciliated cells in many tissues, including kidney tubule. Mutations in *DNAH5* cause a genetic disorder associated with polycystic kidney diseases. *TRIO* encodes a GDP to GTP exchange factor promoting the reorganization of the actin cytoskeleton, thereby playing a role in cell migration and growth. *TRIO* is highly expressed in podocytes and regulates the attachment of podocytes to glomerular basement membrane. *TRIO* also induces Rac 1 activity, which contributes to podocyte injury and proteinuria. *DNAH5*, or *TRIO*, or both could be involved in the mechanism of bevacizumab-induced proteinuria. Interestingly, our functional bioinformatic analysis that rs429023, in moderate LD with rs339947, is an eQTL increasing *TRIO* expression in the glomerulus (Table 14), potentially pointing towards *TRIO* as the putative gene of proteinuria.

Table 14. Bioinformatic analysis of rs13135230, rs2350620, and rs6770663 associated with hypertension, rs339947, rs12482855 and rs408130 associated with proteinuria, rs11662763 associated with composite toxicity, and SNPs in complete LD ($R^2=1.0$) according to LDlink.

Data from Genome Browser, Regulome DB and/or HaploReg v4								
SNPs	eQTL	Region	Regulome DB Score	ChIP-seq	Transcription factor binding motifs	DNaseI sensitivity region	Chromatin state	Histone markers
Hypertension								
rs13135230	-	3.8 kb 3' from <i>LCI2</i>	No data	-	-	-	-	-
rs2350620	-		4	FOXA1	-	-	-	-
rs35026059	-		2c	CTCF	CTCF	-	-	-
rs28695823	-	<i>ASPH</i> intron 14	5	SMARCC1	-	Yes (fetal heart)	Enhancers (HUVEC, aorta and fetal heart)	H3K4me1, H3K4me3, H3K27ac, H3K9ac (HUVEC and heart tissue group)
rs6770663	-	<i>KCNAB1</i> intron 1	6	-	-	-	-	H3K4me1 (HUVEC and aorta)
Proteinuria								
rs339947	-	73 kb 5' from <i>DNAH5</i> 130 kb 5' from <i>TRIO</i>	4	USF1	-	-	Repressed polycomb (HUVEC)	-
rs408130	-		No data	-	-	-	-	-
rs418173	-	60 kb 5' from <i>DNAH5</i> 140 kb 5' from <i>TRIO</i>	5	-	-	-	-	-
rs429023	<i>TRIO</i> in glomerulus (NES=2.1, p=0.039)		5	EBF1	-	-	-	-
rs12482855	-	4.7 kb from <i>RIPK4</i> 5'	No data	-	-	-	-	H3K4me1 (fetal kidney)
Composite toxicity								
rs11662763	<i>EPB41L3</i> in glomerulus (NES=2.8, p=0.0055)	33 kb 3' from <i>TTM4</i>	No data	-	-	-	-	-

[0146] For **Table 14**, SNPs in bold are the selected SNPs from our study and the SNPs not in bold are SNPs in LD with them. Expression quantitative trait loci (eQTL) information was retrieved from the GTEx v7 and NephQTL. The RegulomeDB score represents the evidence that a variant has a regulatory function (1-strong evidence, 6-weak evidence). Data from Genome Browser, RegulomeDB and/or HaploReg v4 includes computational and experimental data from ENCODE and Roadmap Epigenomics Consortium. Only ChIP-seq and transcription binding motifs from experimental data are reported. Only DNaseI sensitivity region, chromatin state and histone markers for relevant cell lines (HUVEC or heart tissue group) are reported. Composite toxicity is defined as the occurrence of either proteinuria or hypertension or both. NES: normalized effect size.

[0147] In addition to *TRIO*, *RIPK4* is also another putative new gene for proteinuria. *RIPK4* (selected by rs12482855, 4.7 kb 5') encodes a protein kinase that interacts with PKC δ , which is directly involved in renal damage by inducing apoptosis in podocytes and also in tubular cells. Finally, *IL17F* codes for interleukin-17F (IL-17F) and was selected by the gene based analysis. Using induced-nephrotoxic nephritis mouse model, IL-17F-deficient mice showed less severe nephritis, with lower albuminuria and better renal function, compared with wild-type mice. *IL17F* was the second most significant gene in our gene-based analysis after *C1D*, the biology of which cannot be reconciled with kidney damage by bevacizumab. Two less common variants (rs1413920 and rs763780, that did not pass the QC MAF<0.05 in SNP-based analysis) are driven the effect of *IL17F* in gene-based analysis. The G allele of rs1413920 (A>G, p=1.80x10⁻⁷, (β=2.24, MAF 0.01-0.03) and of rs763780 (A>G, p=1.14 x10⁻⁴, (β=1.41, MAF 0.05) decreased the risk of proteinuria. rs1413920 is intergenic located 1.3kb 3' from *MCM3* and 20 kb from *IL17F* (**FIG. 8**), with strong transcription in HUVEC. rs763780 is a non-synonymous variant that alters the histidine to arginine at amino acid 161 (H161R). The A allele (161H) has been associated with an anti-angiogenic effect by inhibition the angiogenesis in human endothelial cells. Inversely, patients who present the G allele (161R) could have an enhanced angiogenesis in these cells and be more prone to bevacizumab effect. The G allele was already associated with a better overall survival in CALGB 80303.

[0148] This study also proposes *ASPH* (selected by rs2350620, intronic, and by the gene-based 30 analysis) as novel candidate of bevacizumab-induced hypertension. *ASPH* encodes the junctin protein that forms a quaternary complex with triadin, calsequestrin and the ryanodine receptor (RyR), involved in the release of Ca²⁺ from endoplasmic/sarcoplasmic reticulum. rs2350620 reduced the risk of bevacizumab-induced hypertension and has variants in complete

LD that are located in regions of DNaseI sensitivity, chromatin state enhancers and enriched for histone modifications in HUVEC and cells from heart tissue group. The G allele of rs2350620 is likely to bind FOXA1 protein (in T-47D), which acts as a transcriptional activator. Therefore, rs2350620 might increase *ASPH* expression, which might contribute to confer a reduced risk of hypertension. Moreover, one of the variants in LD (rs35026059, $\rightarrow$ T) has 2c Regulome DB score (Table 14), due to strong evidence of binding of the T allele to CTCF motif, but not in relevant cell lines. CTCF can acts as a transcriptional activator or repressor and insulator.

[0149] Because genetic variants might have pleiotropic effects and hypertension and proteinuria share a common pathophysiology, we have also investigated the occurrence of the composite toxicity. rs11662763 had the same direction of effect in three trials, increasing the risk of either proteinuria or hypertension or both. rs1166276 is 33 kb from *TTMA*, also known as TMEM200C. rs11662763 was shown to be an eQTL for EPB41L3 in the glomerulus, increasing its expression (Table 14). *EPB41L3* was also identified as a novel locus for kidney function, after an intronic SNP (rs9962915) was associated with lower glomerular filtration rate in a GWAS meta-analysis of more than 100,000 subjects. Furthermore, *SLC25A24* was also selected by the gene-based analysis of the composite toxicity. SLC25A24 encodes a carrier protein that transports ATP-Mg exchanging it for phosphate.

[0150] The three most significant variants associated with composite toxicity (rs17084411, rs1927869 and rs17084371) had a p-value of $4.24\text{--}7.24 \times 10^{-8}$ but only in CALGB 40503.

[0151] In conclusion, as a result of this study, *DNAH5*, *TRIO*, *RIPK4*, *IL17F*, *ASPH*, *TTMA*, *EPB41L3* and *SLC25A24*, as well as all the top significant SNPs and genes associated with grade ≥ 3 toxicities are proposed as new genes involved in bevacizumab-induced proteinuria and hypertension. Despite many years of use of bevacizumab, proteinuria and hypertension still represent an obstacle to full delivery of effective therapy, and pose a threat for patients and their quality of life. Because these toxicities are also shared by many other anti-angiogenesis drugs, the availability of these results in the public domain will incentivize the application of these findings to other drugs with a similar mechanism of action.

Example 2

[0152] Sorafenib is an orally administered multikinase inhibitor that targets multiple tyrosine kinases involved in angiogenesis, apoptosis, and tumor cell proliferation, including the vascular endothelial growth factor receptor 2 (VEGFR2). It is approved by the U.S. Food and Drug

Administration (FDA) for the treatment of several tumors, including metastatic renal cell carcinoma (mRCC), advanced hepatocellular carcinoma and differentiated thyroid cancer. The clear-cell histology of RCC is characterized by overexpression of VEGF, which interacts with VEGFR2 to stimulate tumor angiogenesis. In addition to sorafenib, sunitinib, pazopanib, axitinib, lenvatinib and cabozantinib are also approved for mRCC, sharing the same mechanisms of VEGF-pathway inhibition.

[0153] Hypertension is one of the most frequent toxicities induced by sorafenib. A meta-analysis showed a prevalence of sorafenib-induced all-grade and grade ≥ 3 hypertension of 19.1% and 4.3%, respectively. Patients with mRCC experience higher rates of hypertension when compared to other tumor types (all-grade: 24.9% vs 15.7%, high-grade: 8.6% versus 1.8%). Similar to sorafenib, other VEGF-pathway inhibitors can also induce hypertension, including bevacizumab, sunitinib and pazopanib.

[0154] The objective of this study was to identify and validate genetic biomarkers that are predictive of VEGF-pathway inhibitor-induced hypertension using a two-step, discovery-validation approach. Sorafenib-treated patients from the phase 3 Treatment Approaches in Renal Cancer Global Evaluation Trial (TARGET) were used as the discovery set, while a genome-wide association study (GWAS) of bevacizumab-treated patients from four Cancer and Leukemia Group B (CALGB, now Alliance for Clinical Trials in Oncology, Alliance) studies was used as a validation set.

[0155] TARGET was a double-blind, randomized, placebo-controlled phase III trial of patients with mRCC treated with 400 mg sorafenib orally twice daily or placebo. Hypertension was recorded according to CTCAE version 3.0. This analysis was conducted in patients who received at least one cycle (28 days) of sorafenib treatment. DNA was obtained from the peripheral blood of 140 patients treated with sorafenib. A total of 1,536 SNPs in 56 candidate genes were genotyped using the Illumina GoldenGate assay. Genes were selected based upon biological function, including genes involved in VEGF-pathway signaling, genes from additional signaling pathways targeted by sorafenib, genes associated with pericyte survival, sorafenib disposition and toxicity, and genes associated with RCC prognosis/pathogenesis or general cancer prognosis. SNPs were excluded if the genotype call rate was $<97.5\%$ and were selected based upon a MAF >0.05 in Europeans from the 1,000 Genomes Project, and other criteria.

[0156] A flowchart showing the quality control for the study is provided as **FIG. 9A**. After quality control, a total of 973 of the 1,536 initial SNPs were used in this study. Tests for association between SNPs and grade ≥ 2 hypertension were performed in the sorafenib arm by

calculating the odds ratio (OR) from a logistic regression analysis, where grade ≥ 2 hypertension was the binary outcome and SNPs were the independent variables, under an additive model. Age and gender were used as covariates. A p -value ≤ 0.01 was used as a feature selection to identify SNPs for replication in the validation set.

[0157] For the validation cohort, the association between SNPs and hypertension was tested in genetic European patients treated with bevacizumab. A GWAS of four randomized phase III clinical trials from the CALGB/Alliance (CALGB 80303, 40503, 90401, and 40502) was used as the validation set. The details of the individual studies are described in **Table 15**. Patient eligibility, characteristics, stratifications and treatments can be found in the individual publications for all four trials. Blood pressure was measured on day 1 of each cycle in all four trials (and on day 15 in CALGB 80303), and hypertension was recorded according to CTCAE version 3.0. Bevacizumab-induced hypertension was defined as the occurrence of grade ≥ 2 hypertension after the start of treatment. DNA was obtained from peripheral blood. The genotyping platforms used in each study are described in **Table 15**. A cause-specific Cox model, where the outcome was defined as the pair of time event and the censoring indicator (defined as the time from the first administration of bevacizumab to the first incidence of the toxicity of interest, or other treatment-terminating events, whichever occurred first, under a competing risk model), was fitted to obtain the estimate of the SNP effect on hypertension in each individual study. The analyses were powered against an additive genetic model. The inverse variance formula was used to combine the SNP effect in each study to obtain the estimate (β) of the SNP-hypertension association. Age and sex were added as covariates in the model. The exponential function of β was used to calculate OR.

[0158] The SNPs from the TARGET study (discovery set) associated with grade ≥ 2 hypertension (p -value ≤ 0.01) were tested in the CALGB GWAS (validation set). If the variant was not genotyped in the validation set, a SNP in high linkage disequilibrium (LD, $R^2 > 0.8$, Europeans in the 1,000 Genomes Project) according to LDlink, was selected for testing. In the validation set, SNPs with a p -value ≤ 0.01 for association and the same direction of effect (increased or reduced risk) were considered as validated.

[0159] Functional annotation of SNPs was performed using the SCAN database. LDlink was used for analyses of LD. RegulomeDB and SNPnexus were used for functional inference. The Genotype-Tissue Expression project (GTEx v7) was used for expression quantitative trait loci (eQTL) analysis. atSNP was also used to quantify impact of SNPs on transcription factor binding.

[0160] A total of 140 mRCC patients treated with sorafenib in TARGET were included in this study. The characteristics of the patients, and the prevalence of grade ≥ 2 hypertension are shown in Table 15. Variants rs444904 (G>A, MAF 0.14) and rs1346563 (C>T, MAF 0.30) were both selected for testing in the validation set based on $p < 0.01$ (Table 16). Both variants were associated with an increased risk of grade ≥ 2 hypertension (OR=3.88, 95%, CI 1.54-9.81, $p=0.0057$ and OR=3.50, 95%, CI 1.48-8.24, $p=0.0064$, respectively) (Table 16).

Table 15. Patient characteristics and trials.

		Discovery set (n=140)	Validation set (n=1,041)			
Trial		TARGET	CALGB 80303 n=154	CALGB 40503 n=105	CALGB 90401 n=316	CALGB 40502 n=466
Hypertension (n, %)						
Grade ≥ 2		12 (8.6)	26 (16.9)	53 (50.5)	47 (15.0)	143 (30.7)
Grade 3		5 (3.6)	19 (12.3)	29 (27.6)	22 (7.0)	50 (10.7)
Age – Mean (SD)		59.6 (9.8)	64.1 (10.2)	68.4 (8.3)	56.9 (11.7)	57.2 (10.7)
Gender	Male	105	90	0	105	0
	Female	35	64	316	0	466
Cancer type		Advanced and metastatic renal cell carcinoma	Advanced pancreatic cancer	Hormone receptor-positive advanced-stage breast cancer	Metastatic castration-resistant prostate cancer	Recurrent or metastatic breast cancer
Treatment		Sorafenib 400 mg orally twice daily administered in 6-week cycles for the first 24 weeks and in 8-week cycles thereafter	Gemcitabine 1,000 mg/m ² on days 1, 8, and 15 plus either placebo or bevacizumab 10 mg/kg on days 1 and 15	Letrozole 2.5 mg orally/day plus either placebo or bevacizumab 15 mg/kg every 21 days	Docetaxel 75 mg/m ² in combination with prednisone 5 mg orally on day 1 plus either placebo or bevacizumab 15 mg/kg every 21 days	Paclitaxel 90 mg/m ² or nab-paclitaxel 150 mg/m ² or ixabepilone 16 mg/m ² on days 1, 8, and 15 plus bevacizumab 10 mg/kg on days 1 and 15
Genotyping platform		Illumina GoldenGate	Illumina HumanHap550-Quad	Illumina HumanOmniExpressExome-8	Illumina HumanHap610-Quad	Illumina HumanOmniExpressExome-8

Table 16. SNPs associated with sorafenib-induced hypertension in the TARGET study.
The SNPs in bold are the ones tested in the validation ($p \leq 0.01$). Results are shown for associations with p -value < 0.05 , adjusted for age and gender. Chr: chromosome, NA: Intergenic SNP, MAF: minor allele frequency, OR: odds ratio, SNP: single nucleotide polymorphism.

SNP	Chr	Gene	Feature	5' Flanking gene	3' Flanking gene	Base change	MAF	OR (95% CI)	p-value
rs444904	17	<i>PIK3R5</i>	Intron	<i>PIK3R6</i>	<i>LOC100129978</i>	G>A	0.14	3.88 (1.54-9.81)	0.0057
rs1346563	16	<i>ADAMTS18</i>	Intron	<i>VN2R10P</i>	<i>NUDT7</i>	C>T	0.30	3.50 (1.48-8.24)	0.0064
rs2330951	7	<i>EGFR</i>	Intron	<i>LOC643168</i>	<i>LOC100133256</i>	A>C	0.23	4.23 (1.78-10.05)	0.0118
rs11125039	2	<i>PRKCE</i>	Intron	<i>SRBD1</i>	<i>EPAS1</i>	A>G	0.24	3.51 (1.49-8.25)	0.0122
rs56367980	7	<i>EGFR</i>	Intron	<i>LOC643168</i>	<i>LOC100133256</i>	G>A	0.12	3.33 (1.27-8.76)	0.0188
rs16917099	10	NA	NA	<i>RTKN2</i>	<i>ZNF365</i>	T>C	0.13	3.58 (1.37-9.35)	0.0207
rs2740761	7	<i>EGFR</i>	Intron	<i>LOC643168</i>	<i>LOC100130121</i>	C>T	0.18	3.46 (1.39-8.59)	0.0222
rs3754565	2	<i>PRKCE</i>	Intron	<i>SRBD1</i>	<i>EPAS1</i>	G>T	0.11	4.07 (1.48-11.19)	0.0222
rs3754566	2	<i>PRKCE</i>	Intron	<i>SRBD1</i>	<i>EPAS1</i>	G>A	0.11	4.07 (1.48-11.19)	0.0222
rs4596024	2	<i>PRKCE</i>	Intron	<i>SRBD1</i>	<i>EPAS1</i>	A>G	0.11	4.07 (1.48-11.19)	0.0222
rs251312	5	NA	NA	<i>NLN</i>	<i>ERBB2IP</i>	C>T	0.48	3.26 (1.31-8.14)	0.0223
rs12366035	11	<i>VEGFB</i>	reference	<i>DNAJC4</i>	<i>FKBP2</i>	C>T	0.34	3.09 (1.31-7.24)	0.0227
rs35539903	4	<i>KDR</i>	Intron	<i>LOC100132311</i>	<i>LOC100128865</i>	A>G	0.15	3.44 (1.33-8.90)	0.0254
rs35597368	4	<i>PDGFRA</i>	Missense	<i>LOC442108</i>	<i>KIT</i>	T>C	0.10	3.69 (1.32-10.29)	0.0256
rs3797102	5	<i>FLT4</i>	Intron	<i>SCGB3A1</i>	<i>OR2AI1P</i>	T>C	0.42	2.78 (1.17-6.59)	0.0262
rs3804158	4	<i>NUDT6/FGF2</i>	Intron/ UTR-3	<i>BBS12</i>	<i>SPATA5</i>	A>G	0.43	0.30 (0.11-0.84)	0.0272
rs45492196	1	<i>PIK3C2B</i>	Reference	<i>PPP1R15B</i>	<i>LOC100130573</i>	G>A	0.05	3.68 (1.07-12.60)	0.0279
rs7187665	16	<i>WWOX</i>	Intron	<i>LOC100131126</i>	<i>LOC645947</i>	T>C	0.45	0.34 (0.13-0.89)	0.0298
rs11980616	7	<i>GNAI1</i>	Intron	<i>LOC100128030</i>	<i>GNAT3</i>	A>G	0.13	3.24 (1.24-8.50)	0.0322
rs659441	3	NA	NA	<i>UMPS</i>	<i>ITGB5</i>	G>C	0.40	0.28 (0.11-0.73)	0.0327
rs315498	17	NA	NA	<i>LOC100130112</i>	<i>C17orf79</i>	T>C	0.33	0.24 (0.07-0.84)	0.0335
rs41348645	4	<i>FGF2/NUDT6</i>	UTR-3/ Intron	<i>BBS12</i>	<i>SPATA5</i>	G>A	0.41	0.31 (0.11-0.87)	0.0350
rs3950680	11	<i>PIK3C2A</i>	Intron	<i>RPS13</i>	<i>LOC732199</i>	G>A	0.36	2.61 (1.12-6.06)	0.0385
rs6743202	2	<i>TGFA</i>	Intron	<i>LOC100128042</i>	<i>ADD2</i>	A>T	0.32	0.27 (0.08-0.93)	0.0421
rs11644322	16	<i>WWOX</i>	Intron	<i>LOC645947</i>	<i>LOC729251</i>	C>T	0.21	2.66 (1.10-6.42)	0.0431
rs446086	2	<i>TGFA</i>	Intron	<i>LOC100128042</i>	<i>ADD2</i>	C>A	0.23	0.19 (0.04-0.84)	0.0431
rs3804452	6	<i>MAPK14</i>	utr-3	<i>SLC26A8</i>	<i>MAPK13</i>	C>T	0.11	2.86 (1.04-7.84)	0.0439
rs2293348	7	<i>EGFR</i>	Intron	<i>LOC100133256</i>	<i>LOC100130121</i>	G>A	0.36	0.32 (0.11-0.96)	0.0466
rs16947173	16	<i>WWOX</i>	Intron	<i>LOC100131126</i>	<i>LOC645947</i>	A>G	0.20	0.12 (0.02-0.93)	0.0480
rs11644207	16	<i>WWOX</i>	Intron	<i>LOC100131126</i>	<i>LOC645947</i>	T>G	0.24	0.22 (0.05-0.64)	0.0484
rs8193040	6	NA	NA	<i>IL17A</i>	<i>LOC730141</i>	T>G	0.48	0.39 (0.16-0.97)	0.0499

[0161] A total of 1,041 patients treated with bevacizumab in the CALGB trials were included in this study. Because neither rs444904 nor rs1346563 were genotyped on the GWAS platforms, rs427554 (G>A, MAF 0.10-0.11 in complete LD $R^2=1.0$ with rs444904) and rs4888628 (A>G, MAF 0.26-0.29, LD $R^2=0.96$ with rs1346563) were used as proxies. Variant rs427554 was associated with an increased risk of hypertension ($p=0.008$, $\beta=0.33$, OR=1.39, CI 1.09-1.78) (FIG. 10). This result is consistent with the discovery set, where the frequencies of patients without hypertension with the AA and GA genotypes are 2.3% and 20.3%, respectively, versus 25.0% and 16.7% in patients with hypertension (FIG. 9B).

[0162] Table 17 provides bioinformatic analyses for both rs444904 and rs427554. There is evidence in GTex that rs444904 and rs427554 are both eQTLs for *PIK3R5* in whole blood, with the A allele of both variants associated with decreased gene expression. DNase 1 hypersensitivity peaks indicate that both rs444904 and rs427554 are located in areas of open

chromatin, thus permitting selective binding of transcription factors, while ChIP-seq revealed that the two SNPs are potential loci for binding with putative transcription factors. RegulomeDB, utilizing data from the ENCODE-motif database, indicates that rs427554 is located in the binding motif for the SP1 transcription factor. Additional data from the JASPAR database (using atSNP) predicts preferential binding of SP1 to the G allele of rs444904 rather than the A allele ($p=0.01$ for the G allele, and $p=0.30$ for the A allele). The majority of non-coding variation scores provided by SNPnexus shows a higher evidence of regulatory function of rs427554 compared to rs444904 (Table 17).

Table 17. Bioinformatic analysis of rs444904 and rs427554. The RegulomeDB score represents the evidence that a SNP has a regulatory function (1-strong evidence, 6-weak evidence). SNPnexus non-coding variation scoring predicts functional impact of non-coding SNPs using 8 non-coding SNP scoring algorithms. Higher scores in CADD (range 0-99), FitCons (range 0-1), Eigen (range 0-1), FATHMM (range 0-1), GWAFA (3 scores, range 0-1), funSeq2 (range 0-5) ReMM (range 0-1) mean that the SNP is most likely to be functional/deleterious, while a lower score in DeepSEA (range 0-1) means that the SNP is most likely to be functional/deleterious. eQTL: expression quantitative trait loci, NES: normalized effect size

SNP (Regulome DB score)	eQTL (GTEx)	RegulomeDB/ ENCODE		SNPnexus non-coding variation rankings								
		ChIP-seq	DNase I Sensitivity region	Motif	CADD	FitCons	EIGEN	FATHMM	GWAVA	DeepSEA	FunSeq2	ReMM
rs444904 (4)	Whole blood (p=2.7x10 ⁻¹² , NES=-0.16)	POLR2A, RELA, EP300, TCF12, EBF1, IKZF2, IKZF1, TAF1, MEF2C, TBL1XR1, FOXM1, ZNF687, TARDBP, NFATC1, MTA3, ZEB1, MTA2, YY1, CBFB, RUNX3, GATAD2B, CHD2, ELF1, BCLAF1, ETS1, ARNT, EGR1, IRF4, PBX3, TCF7, NFIC, BHLHE40, POU2F2, CREM, BCL3, MEF2A, ETV6.	Yes	-	0.775	0.102	0.176	0.110	0.38/ 0.48/ 0.44	0.035	1.560	0.019
rs427554 (2c)	Whole blood (p=9.4x10 ⁻¹³ , NES=-0.17)	POLR2A, GATA1, SPI1, IKZF1, IKZF2, ZBTB40, TCF7, MLLT1, EP300, ELF1, LEF1, PAX5, BCLAF1, DPF2, TRIM22, RELB, ARNT, MXI1, FOXM1, NR2F1, SMARCA5, ZMYM3, SPI1, MEF2A, RBM25, TARDBP, NBN, TAF1, BHLHE40, BCL3, RUNX3, KLF5, BATF, ETV6, NFATC3, ZFXH2, ZBTB33, ETS1, IRF4, NKRF, VEZF1, ZBED1, SKIL, ZNF207, CREM, ETV1, CBFB, HDGF, TBX21, ARID3A, BCL11A, POU2F2, EGR1, COMMD3-BMI1, BMI1, ATF2, REST, RFX1, MAZ, EBF1, ZNF143, FFD.	Yes	SP1	2.641	0.102	0.614	0.141	0.45/ 0.53/ 0.41	0.118	1.560	0.122

[0163] The results of the study identified a common intronic SNP (rs444904) located in *PIK3R5* that increased the risk of grade ≥ 2 hypertension in patients treated with the VEGF-pathway inhibitors sorafenib and bevacizumab.

[0164] Bioinformatic analyses of rs444904 and rs427554 in *PIK3R5* showed that both SNPs are located in a region that binds numerous transcription factors, indicating a potential regulatory role for each SNP in gene expression (Table 17). rs427554 is located within a binding motif for SP1, and rs444904 may alter an SP1 binding motif as described above. Considering that both SNPs are in complete LD with each other, it is plausible to suggest that the G allele of both variants may increase binding of the SP1 transcription factor to DNA.

[0165] In embodiments, the data provided herein proposes a novel mechanism through which rs444904 and rs427554 regulate the expression of *PIK3R5* and mediate hypertension induced by sorafenib, bevacizumab, or other VEGF pathway inhibitors. The G allele of both SNPs allows the binding of SP1, which, by inhibiting the action of DNMT, activates *PIK3R5* transcription (FIG. 12). Conversely, the A allele decreases the binding of the SP1, which allows DNA methylation by DNMT, downregulating *PIK3R5* transcription, (FIGs. 11 and 12).

[0166] The validation of rs444904 in an external dataset utilizing a different VEGF-pathway inhibitor (such as bevacizumab) provides additional evidence of clinical applicability of biomarkers of hypertension induced by different anti-angiogenic drugs. Taken together, the study provides evidence for rs444904 in *PIK3R5* as a biomarker of hypertension induced by sorafenib, bevacizumab, and other VEGF pathway inhibitors. Common genetic variants in *PIK3R5*, rs444904 and rs427554 in complete LD with each other ($R^2=1.00$), increased the risk of sorafenib and bevacizumab-induced hypertension in two independent datasets, and may be used as predictor biomarkers of hypertension induced by the whole class of VEGF-pathway inhibitors

Example 3

[0167] Two SNPs associated with grade ≥ 2 hypertension in Example 1 above, rs2350620 and rs6770663, were evaluated for replication in European ancestry patients from ECOG-ACRIN E5103. A summary of the cohort evaluated is provided as Table 18.

Table 18. GWAS patients of European ancestry treated with bevacizumab from ECOG-ACRIN E5103. ECOG Eastern Cooperative Oncology Group, ACRIN American College of Radiology Imaging Network, SBP systolic blood pressure, SD standard deviation.

	Validation set ECOG-5103	
	SBP $\geq$ 160mm Hg <i>n</i> =582	Grade $\geq$ 3 <i>n</i> =564
Hypertension* (<i>n</i> , %)	195 (33.5)	177 (37.8)
Age – Mean (SD)	55.3	55.1
Gender		
Male	0	0
Female	582	564
Cancer type	Breast cancer	
Treatment	Doxorubicin (60 mg/m ²) and cyclophosphamide (600 mg/m ²) for four cycles, followed by 12 weeks (4 cycles) of weekly paclitaxel. Concurrently to chemotherapy, patients received either placebo (arm A) or bevacizumab 10-15 mg/kg (arms B and C). Patients in arm C continued bevacizumab monotherapy (15 mg/kg every 3 weeks) for an additional 10 cycles.	
Genotype platform	Illumina Human Omni1-Quad and Illumina Human OmniExpress	

[0168] Variants rs2350620 and rs6770663 were selected because they were among the top ten SNPs that also had a concordant effect in three out of four studies (p -value <0.05 for each study) (Table 5). FIG. 13 shows the cumulative incidence of grade ≥ 2 hypertension for rs2350620 and rs6770663. Table 19 shows the results of the SNPs tested for replication. The G allele of rs6770663 (A>G, MAF 0.08-0.09) was associated with a higher risk of SBP ≥ 160 mm Hg (odds ratio, OR=1.76, p -value=0.005) in ECOG-ACRIN E5103 (Table 20), similar to the increased risk of grade ≥ 2 hypertension in our study ($\beta=0.57$, p -value= 4.79×10^{-6}) (Table 5).

Table 19. Top two SNPs ranked by unadjusted p -value with a concordant effect in three out of four studies for grade ≥ 2 hypertension in the CALGB trials tested for replication in the ECOG-ACRIN E5103 GWAS. ECOG Eastern Cooperative Oncology Group, ACRIN American College of Radiology Imaging Network, MAF minor allele frequency, SBP systolic blood pressure, OR odds ratio. The row in bold is the one SNP that replicated in ECOG-ACRIN E5103.

SNP	Risk allele	MAF ECOG-ACRIN E5103	OR (SBP $\geq$ 160 mm Hg)	p -value (SBP $\geq$ 160 mm Hg)
Grade ≥ 2				
rs2350620	T	0.33	1.14	0.235
rs6770663	G	0.10	1.76	0.005

Table 20. Frequency of rs6770663 AA, GA, and GG genotypes associated with bevacizumab-induced hypertension in ECOG-ACRIN E5103. ECOG Eastern Cooperative Oncology Group, ACRIN American College of Radiology Imaging Network, SBP systolic blood pressure.

	rs6770663		
	AA	GA	GG
SBP ≥160 (cases, <i>n</i> =195)	147 (75.4%)	45 (23.1%)	3 (1.5%)
No hypertension (controls, <i>n</i> =387)	327 (84.5%)	59 (15.2%)	1 (0.3%)

[0169] Table 21 shows published studies that reported associations between 37 SNPs and bevacizumab-induced hypertension with *p*-value<0.05. Out of 37 SNPs, 26 of them had either the same SNP or a proxy for it. Three out of the 26 SNPs were associated with composite toxicity (but with neither hypertension nor proteinuria) with the same direction of the effect (either reduced or increased risk) in the herein provided study (Table 22).

Table 21. SNPs previously associated with bevacizumab-induced hypertension in the literature. *VEGF* vascular endothelial growth factor, *NO* nitric oxide, *CTCAE* Common Toxicity Criteria for Adverse Events, *FOLFIRI* 5-fluorouracil (5-FU) + irinotecan, *FOLFOX* 5-FU + oxaliplatin, *XELOX* capecitabine + oxaliplatin, *SBP* systolic blood pressure. Not on platform means that either the reported SNP or SNPs in high LD ($R^2>0.8$) were not on the genotype platforms in our study.

Reference	SNP selection method	Genes associated	Hypertension phenotype	Concomitant treatment	Number of bevacizumab treated patients	Clinical trial discovery set
Li et al. (2018)	Sequencing of 174 candidate genes (VEGF signaling, endothelial cell biology, NO signaling or essential hypertension genes)	<i>HSP90AB1</i> <i>PRKCA</i> <i>CACNA1C</i> <i>HSP90AB1</i> <i>CCL2</i> <i>PDE3B</i> <i>NOSIP</i> <i>FLT4</i>	Grade ≥3 (CTCAE v3.0)	FOLFIRI or FOLFOX6	61	Discovery: CALGB 80405 Validation: CALGB 40502, CALGB 90401, and ECOG-5103
Frey et al. (2017)	103 SNPs in 11 genes (VEGF and essential hypertension associated genes)	<i>GRK4</i> <i>KLKB1</i> <i>VEGF</i> <i>WINK1</i>	Grade ≥1 (CTCAE v3.0)	Cisplatin and taxotere/ doxorubicin, and cyclophosphamide/ paclitaxel and cisplatin/ erlotinib/ letrozole/ S-1 and oxaliplatin	114	6 clinical trials at Memorial Sloan-Kettering Cancer Center
Berger et al. (2017)	12 SNPs in 8 autophagy-related genes	<i>FIP200</i> <i>ATG13</i>	Grade ≥2 (CTCAE v3.0)	FOLFIRI	219	TRIBE

Gampenrieder et al. (2017)	10 SNPs in <i>VEGFA</i> , <i>FLT1</i> , <i>STK39</i> , <i>EDN1</i> , and <i>UMOD</i>	<i>VEGFA</i>	Grade ≥ 3	Capecitabine or taxane	163	Retrospective selection of patients from hospital records
Sibertin-Blanc et al. (2015)	10 SNPs in <i>VEGFA</i> , <i>FLT1</i> , <i>KDR</i> , and <i>HIF1A</i>	<i>VEGFA</i>	Grade ≥ 1 (CTCAE v3.0)	5-FU based chemotherapy (the majority FOLFIRI)	89	Retrospective selection of patients from hospital records
Lambrechts et al. (2014)	236 SNPs in 14 genes (VEGF and essential hypertension associated genes).	<i>EGLN3</i> <i>KDR</i> <i>EPAS1</i> <i>FLT1</i> <i>FLT4</i> <i>EGF</i> <i>WINK1</i>	Grade ≥ 1 (CTCAE v3.0)	XELOX or FOLFOX4/ gemcitabine and erlotinib/ cisplatin and gemcitabine/ interferon α -2a/ docetaxel/ capecitabine and cisplatin	807	NO16966, AVITA, AVAIL, AVOREN, AVADO, AVAGAST
Morita et al. (2013)	5 SNPs in <i>VEGFA</i>	<i>VEGFA</i>	Grade ≥ 2 (CTCAE v4.0)	FOLFIRI or FOLFOX6 or 5-FU or XELOX	60	Retrospective selection of patients from hospital records
Etienne-Grimaldi et al. (2011)	5 SNPs in <i>VEGFA</i>	<i>VEGFA</i>	Grade ≥ 1 (CTCAE v3.0)	Paclitaxel or docetaxel or navelbine	137	ATHENA
Schneider et al. (2008)	7 SNPs in <i>VEGF</i> and <i>KDR</i>	<i>VEGFA</i>	Grade ≥ 3 (CTCAE v2.0)	Paclitaxel	180	ECOG-2100

Table 22. Previously reported variants associated with bevacizumab-induced hypertension. The associations with a p -value < 0.05 and same direction of effect for grade ≥ 2 composite toxicity in our study are shown. Proxy rs9900205 was genotyped only in CALGB 90401, and proxy rs833070 was genotyped only in CALGB 40503.

SNP (literature)	Region	Base change	Risk (literature)	Risk (our study)
rs59189065	<i>PRKCA</i> intronic	G>A	Increased grade ≥ 3 hypertension in CALGB 80405	Proxy rs9900205 ($R^2=0.82$) Increased grade ≥ 2 composite toxicity in CALGB 90401 ($\beta=0.49$, $p=0.02$)
rs9381299	3 kb 5' from HSP90AB1 and 10 kb 3' from of SLC29A1	T>C	Increased grade ≥ 3 hypertension in CALGB 80405 (discovery set), and in CALGB 40502 and ECOG 5103 (validation sets), but not in CALGB 90401	Increased grade ≥ 2 composite toxicity in CALGB 80303, 40503, and 90401 ($\beta=0.39$, $p=0.02$)
rs833061	5' of <i>VEGFA</i>	C>T	Decreased grade ≥ 2 (7) and grade ≥ 3 (6) hypertension	Proxy rs833070 ($R^2=0.98$) Decreased grade ≥ 2 composite toxicity in CALGB 40503 ($\beta=-0.44$, $p=0.03$)

[0170] Taken together, the studies provided herein were the largest genome-wide analysis of bevacizumab-induced hypertension and proteinuria, which included 1,041 cancer patients from four randomized phase III clinical trials. The large sample size, randomized design, and standardized collection of the phenotypic and genotypic data facilitated the testing of genetic associations of drug response in patients. The use of genomic data from different studies allowed the evaluation of concordance of the effect, increasing the validity of these associations. For the first time, a variant in *KCNAB1* for bevacizumab-induced hypertension was identified from an independent, external dataset provided and provided evidence of clinical actionability. Accordingly, the results of the study provide a critical identification of SNPs and gene variants that can be used to provide improved and safer methods for treating patients with bevacizumab or other VEGF pathway inhibitor drugs. For example, patients indicated for or being treated with an inhibitor of the VEGF pathway (e.g., bevacizumab) can be assessed for the presence of rs6770663, and treatment modified accordingly (e.g., pre-treatment with anti-hypertensive supportive therapy and/or dose modification and/or delivery of an alternative to the VEGF pathway inhibitor).

[0171] Importantly, the study established replication of the effect of rs6770663 (A>G), intronic in *KCNAB1*, as a variant for the risk of hypertension. Similar to the CALGB studies where it increased the risk of grade ≥ 2 hypertension, rs6770663 was also associated with a higher risk of SBP ≥ 160 mm Hg in ECOG-ACRIN E5103 (Table 14, FIG. 13).

[0172] In addition to *KCNAB1*, the studies provided herein identified other new candidate genes associated with VEGF pathway inhibitor-induced toxicity. This selection was based upon the strength and probability of the associations, the biological plausibility of gene, and the bioinformatic prediction of the SNP effect on the gene function or expression. Under this set of evaluations, *ASPH* was also identified as a new gene for VEGF pathway inhibitor-induced hypertension, based upon the signal of intronic rs2350620 (FIG. 13). Variant rs2350620 (A>G) reduced the risk of bevacizumab-induced hypertension and has SNPs in complete LD located in regulatory regions in HUVEC, aorta and the heart (Table 14). Also, rs2350620 is in complete LD with a deletion in *ASPH* (rs35026059, T>-), and CTCF can act as an insulator of the expression of *ASPH* because of binding in the presence the T allele (Table 14).

[0173] Despite many years of use of bevacizumab, hypertension and proteinuria still represent an obstacle to full delivery of effective therapy and pose a threat for patients and their quality of life. The studies provided herein identified rs6770663 in *KCNAB1* as a novel marker of bevacizumab-induced hypertension that can be used to guide decisions on the risk assessment

of patients treated with any VEGF pathway inhibitor. Other novel candidate genes are *ASPH* for hypertension, and *TRIO* and *DNAH5* for proteinuria. Because these toxicities are also shared by many other antiangiogenesis drugs, the availability of these results in the public domain will expedite their translation into clinical application for other drugs with a similar mechanism of action.

[0174] In summary, the results of the studies provided herein showed that variant rs6770663 in *KCNAB1* was associated with an increased the risk of hypertension ($p=4.79 \times 10^{-6}$). This was validated in ECOG-ACRIN E5103 ($p=0.005$). Variant rs2350620 in *APSH* was associated with a decreased risk of hypertension ($p=1.44 \times 10^{-6}$) and rs339947 (between *DNAH5* and *TRIO*) was associated with an increased risk of proteinuria ($p=7.66 \times 10^{-8}$). Three variants previously associated with bevacizumab-induced hypertension were associated with composite toxicity (but not hypertension) with the same direction of effect in our study. To the knowledge of the inventors, this was the largest GWAS of bevacizumab-treated patients from randomized trials. The study has identified new genes involved in bevacizumab-induced hypertension and proteinuria. Genetic variation in *KCNAB1* can be regarded to as a new validated biomarker to predict the risk of bevacizumab-induced hypertension.

[0175] All literature and similar materials cited in this application, including but not limited to, patents, patent applications, articles, books, treatises, and internet web pages are expressly incorporated by reference in their entirety for any purpose. Unless defined otherwise, all technical and scientific terms used herein have the same meaning as is commonly understood by one of ordinary skill in the art to which the various embodiments described herein belongs. When definitions of terms in incorporated references appear to differ from the definitions provided in the present teachings, the definition provided in the present teachings shall control.

[0176] Various modifications and variations of the described compositions, methods, and uses of the technology will be apparent to those skilled in the art without departing from the scope and spirit of the technology as described. Although the technology has been described in connection with specific exemplary embodiments, it should be understood that the disclosure as claimed should not be unduly limited to such specific embodiments. Indeed, various modifications of the described modes for carrying out the disclosure that are obvious to those skilled in pharmacology, biochemistry, medical science, or related fields are intended to be within the scope of the following claims.

REFERENCES

1. Ferrara N, Adamis AP. Ten years of anti-vascular endothelial growth factor therapy. *Nat Rev Drug Discov* 2016, **15**, 385-403.
2. Ellis LM, Kirkpatrick P. Bevacizumab. *Nat Rev Drug Discov* 2005, **3**, 995-996.
3. Zhu X, Wu S, Dahut WL, Parikh CR. Risks of Proteinuria and Hypertension With Bevacizumab, an Antibody Against Vascular Endothelial Growth Factor: Systematic Review and Meta-Analysis. *Am J Kidney Dis* 2007, **49**, 186-19.
4. Izzedine H, Ederhy S, Goldwasser F, Soria JC, Milano G, Cohen A et al. Management of hypertension in angiogenesis inhibitor-treated patients. *Ann Oncol* 2009, **20**, 807-815.
5. Hurwitz H, Fehrenbacher L, Novotny W, Cartwright T, Hainsworth J, Heim W et al. Bevacizumab plus Irinotecan, Fluorouracil, and Leucovorin for Metastatic Colorectal Cancer. *N Engl J Med* 2004, **350**, 2335-2342.
6. Syrigos KN, Karapanagiotou E, Boura P, Manegold C, Harrington K. Bevacizumab-induced hypertension: pathogenesis and management. *Biodrugs* 2011, **25**, 159-169.
7. Schneider BP, Wang M, Radovich M, Sledge GW, Badve S, Thor A et al. Association of vascular endothelial growth factor and vascular endothelial growth factor receptor-2 genetic polymorphisms with outcome in a trial of paclitaxel compared with paclitaxel plus bevacizumab in advanced breast cancer: ECOG 2100. *J Clin Oncol* 2008, **28**, 4672-4678.
8. Jain L, Sissung TM, Danesi R, Kohn EC, Dahut WL, Kummar S et al. Hypertension and hand-foot skin reactions related to VEGFR2 genotype and improved clinical outcome following bevacizumab and sorafenib. *J Exp. Clin Cancer Res* 2010, **29**, 95.
9. Morita S, Uehara K, Nakayama G, Shibata T, Oguri T, Inada-Inoue M et al. Association between bevacizumab-related hypertension and vascular endothelial growth factor (VEGF) gene polymorphisms in Japanese patients with metastatic colorectal cancer. *Cancer Chemother Pharmacol* 2013, **71**, 405-411.
10. Lambrechts D, Moisse M, Delmar P, Miles DW, Leighl N, Escudier B et al. Genetic markers of bevacizumab-induced hypertension. *Angiogenesis* 2014, **17**, 685-694.
11. Sibertin-Blanc C, Mancini J, Fabre A, Lagarde A, Del Grande J, Levy N et al. Vascular Endothelial Growth Factor A c. 237C T polymorphism is associated with bevacizumab efficacy and related hypertension in metastatic colorectal cancer. *Dig Liver Dis* 2015, **47**, 331-337.

12. Gampenrieder SP, Hufnagl C, Brechelmancher S, Huemer F, Hackl H, Rinnerthaler G et al. Endothelin-1 genetic polymorphism as predictive marker for bevacizumab in metastatic breast cancer. *Pharmacogenomics J* 2017, **17**, 344-350.
13. Etienne-Grimaldi MC, Formento P, Degeorges A, Pierga JY, Delva R, Pivot X et al. Prospective analysis of the impact of VEGF-A gene polymorphisms on the pharmacodynamics of bevacizumab-based therapy in metastatic breast cancer patients. *Br J Clin Pharmacol* 2011, **71**, 921-928.
14. Frey MK, Dao F, Olvera N, Konner JA, Dickler MN, Levine DA et al. Genetic predisposition to bevacizumab-induced hypertension. *Gynecol Oncol* 2017, **147**, 621-625.
15. Schneider BP, Li L, Shen F, Miller KD, Radovich M, O'Neill A et al. Genetic variant predicts bevacizumab-induced hypertension in ECOG-5103 and ECOG-2100. *Br J Cancer* 2014, **111**, 1241-1248.
16. Li M, Kroetz DL. Bevacizumab-induced hypertension: Clinical presentation and molecular understanding. *Pharmacol Ther* 2018, **182**, 152-160.
17. Kindler HL, Niedzwiecki D, Hollis D, Sutherland S, Schrag D, Hurwitz HB et al. Gemcitabine plus bevacizumab compared with gemcitabine plus placebo in patients with advanced pancreatic cancer: Phase III trial of the Cancer and Leukemia Group B (CALGB 80303). *J Clin Oncol* 2010, **28**, 3617-3622.
18. Dickler MN, Barry WT, Cirincione CT, Ellis MJ, Moynahan ME, Innocenti F et al. Phase III trial evaluating letrozole as first-line endocrine therapy with or without bevacizumab for the treatment of postmenopausal women with hormone receptor-positive advanced-stage breast cancer: CALGB 40503 (Alliance). *J Clin Oncol* 2016, **34**, 2602-2609.
19. Kelly WK, Halabi S, Carducci M, George D, Mahoney JF, Stadler WM et al. Randomized, double-blind, placebo-controlled phase III trial comparing docetaxel and prednisone with or without bevacizumab in men with metastatic castration-resistant prostate cancer: CALGB 90401. *J Clin Oncol* 2012, **30**, 1534-1540.
20. Rugo HS, Barry WT, Moreno-Aspitia A, Lyss AP, Cirincione C, Leung E et al. Randomized phase III trial of paclitaxel once per week compared with nanoparticle albumin-bound nab-paclitaxel once per week or ixabepilone with bevacizumab as first line chemotherapy for locally recurrent or metastatic breast cancer: CALGB 40502/NCCTG N063H (Alliance). *J OM Oncol* 2015, **33**, 2361-2369.

21. Innocenti F, Jiang C, Sibley AB, Denning S, Etheridge AS, Watson D et al. An initial genetic analysis of gemcitabine-induced high-grade neutropenia in pancreatic cancer patients in CALGB 80303 (Alliance). *Pharmacogenet Genomics* 2019, **29**, 123-131.
22. Innocenti F, Owzar K, Cox NL, Evans P, Kubo M, Zembutsu H et al. A genome-wide association study of overall survival in pancreatic cancer patients treated with gemcitabine in CALGB 80303. *OM Cancer Res* 2012, **18**, 577-584.
23. Baldwin RM, Owzar K, Zembutsu H, Chhibber A, Kubo M, Jiang C et al. A genome-wide association study identifies novel loci for paclitaxel-induced sensory peripheral neuropathy in CALGB 40101. *OM Cancer Res* 2012, **18**, 5099-5109.
24. Rashkin SR, Chua KC, Ho C, Mulkey F, Jiang C, Mushiroda T et al. A Pharmacogenetic Prediction Model of Progression-Free Survival in Breast Cancer using Genome-Wide Genotyping Data from CALGB 40502 (Alliance). *Clin Pharmacol Ther* 2019, **105**, 738-745.
25. Price AL, Patterson NJ, Plenge RM, Weinblatt ME, Shadick NA, Reich D. Principal components analysis corrects for stratification in genome-wide association studies. *Nat Genet* 2006, **38**, 904-909.
26. European Bioinformatics Institute,
<ftp://ftp.ebi.ac.uk/pub/databases/genenames/new/tsv/locus groups/protein-coding gene.txt>. Accessed on May 7 (2018).
27. Carlson M, Maintainer BP. TxDb.Hsapiens.UCSC.hg18.knownGene: Annotation package for TxDb object(s). R package version 3.2.2. (2015).
28. Carlson M, Maintainer BP. TxDb.Hsapiens.UCSC.hg19.knownGene: Annotation package for TxDb object(s). R package version 3.2.2. (2015).
29. Yi C, Sibley A, Owzar K. snplist: Tools to Create Gene Sets. R package version 0.18.1. (2017).
30. Wu MC, Lee S, Cai T, Li Y, Boehnke M, Lin X. Rare-variant association testing for sequencing data with the sequence kernel association test. *Am J Hum Genet* 2011, **89**, 82-93.
31. Tang ZZ, Lin DY. MASS: Meta-analysis of score statistics for sequencing studies. *Bioinformatics* 2013, **29**, 1803-1805.
32. Zhang W, Gamazon ER, Zhang X, Konkashbaev A, Liu C, Szilagyil KL et al. SCAN database: Facilitating integrative analyses of cytosine modification and expression QTL. *Database* 2015, **27**, bav025.

33. Machiela MJ, Chanock SJ. LDlink: A web-based application for exploring population-specific haplotype structure and linking correlated alleles of possible functional variants. *Bioinformatics* 2015, **31**, 3555-3557.
34. James Kent W, Sugnet CW, Furey TS, Roskin KM, Pringle TH, Zahler AM et al. The human genome browser at UCSC. *Genome Res* 2002, **12**, 996-1006.
35. Boyle AP, Hong EL, Hariharan M, Cheng Y, Schaub MA, Kasowski M et al. Annotation of functional variation in personal genomes using RegulomeDB. *Genome Res* 2012, **22**, 1790-1797.
36. Ward LD, Kellis M. HaploReg: A resource for exploring chromatin states, conservation, and regulatory motif alterations within sets of genetically linked variants. *Nucleic Acids Res* 2012, **40**, D930—D934.
37. GTEx Consortium. The Genotype-Tissue Expression (GTEx) pilot analysis: Multitissue gene regulation in humans. *Science* 2015, **8**, 648-660.
38. Gillies CE, Putler R, Menon R, Otto E, Yasutake KI, Nair V et al. An eQTL Landscape of Kidney Tissue in Human Nephrotic Syndrome. *Am J Hum Genet* 2018, **103**, 232-244.
39. Leigh MW, Pittman JE, Carson JL, Ferkol TW, Dell SD, Davis SD et al. Clinical and genetic aspects of primary ciliary dyskinesia/kartagener syndrome. *Genet Med* 2009, **11**, 473-87.
40. Maier M, Baldwin C, Aoudjit L, Takano T. The role of trio, a rho guanine nucleotide exchange factor, in glomerular podocytes. *Int J Mol Sci* 2018, **19**, E479.
41. Robins R, Baldwin C, Aoudjit L, Cote JF, Gupta IR, Takano T. Rac1 activation in podocytes induces the spectrum of nephrotic syndrome. *Kidney Int* 2017, **92**, 349-364.
42. Yu H, Suleiman H, Kim AH, Miner JH, Dani A, Shaw AS et al. Rac1 Activation in Podocytes Induces Rapid Foot Process Effacement and Proteinuria. *Mol Cell Biol* 2013, **33**, 4755-4764.
43. Li X, Pabla N, Wei Q, Dong G, Messing RO, Wang CY et al. PKC- δ Promotes Renal Tubular Cell Apoptosis Associated with Proteinuria. *J Am Soc Nephrol* 2010, **21**, 1115-1124.
44. Riedel JH, Paust HJ, Krohn S, Turner JE, Kluger MA, Steinmetz OM et al. IL-17F Promotes Tissue Injury in Autoimmune Kidney Diseases. *J Am Soc Nephrol* 2016, **27**, 3666-3677.

45. Starnes T, Robertson MJ, Sledge G, Kelich S, Nakshatri H, Broxmeyer HE et al. Cutting Edge: IL-17F, a Novel Cytokine Selectively Expressed in Activated T Cells and Monocytes, Regulates Angiogenesis and Endothelial Cell Cytokine Production. *J Immunol* 2001, **167**,4137-4140.
46. Oyadomari S, Araki E, Mori M. Endoplasmic reticulum stress-mediated apoptosis in pancreatic (β-cells. *Apoptosis* 2002, **7**, 335-345.
47. Bucci M, Gratton JP, Rudic RD, Acevedo L, Roviezzo F, Cirino G et al. In vivo delivery of the caveolin-1 scaffolding domain inhibits nitric oxide synthesis and reduces inflammation. *Nat Med* 2000, **6**, 1362-1367.
48. 49. Yang YA, Zhao JC, Fong KW, Kim J, Li S, Song C et al. FOXA1 potentiates lineage-specific enhancer activation through modulating TET1 expression and function. *Nucleic Acids Res* 2016, **44**, 8153-8164.
49. Holwerda SJ, de Laat W. CTCF: The protein, the binding partners, the binding sites and their chromatin loops. *Philos Trans R Soc Lond B Biol Sci* 2013, **368**, 20120369.
50. Gorski M, Most PJV, Teumer A, Chu AY, Li M, Mijatovic V et al. Corrigendum: 1000 Genomes-based meta-analysis identifies 10 novel loci for kidney function. *Sci Rep*. 2017, **7**, 46835.
51. De Francesco EM, Maggiolini M, Tanowitz HB, Sotgia F, Lisanti MP. Targeting hypoxic cancer stem cells (CSCs) with Doxycycline: Implications for optimizing anti-angiogenic therapy. *Oncotarget* 2017, **8**, 56126-56142.
52. Calbet JAL. Chronic hypoxia increases blood pressure and noradrenaline spillover in healthy humans. *J Physiol* 2003, **551**, 379-386.
53. Gueler F, Shushakova N, Mengel M, Hueper K, Chen R, Liu X et al. A novel therapy to attenuate acute kidney injury and ischemic allograft damage after allogenic kidney transplantation in mice. *PLoS One* 2015, **10**, e0115709.
54. Chen R, Liliental JE, Kowalski PE, Lu Q, Cohen SN. Regulation of transcription of hypoxia-inducible factor-1α (HIF-1 α) by heat shock factors HSF2 and HSF4. *Oncogene* 2011, **30**, 2570-2580.
55. Huang CY, Pal PY, Kuo CH, Ho TJ, Lin JY, Lin DY et al. p53-mediated miR-18 repression activates HSF2 for IGF-IIR-dependent myocyte hypertrophy in hypertension induced heart failure. *Cell Death Dis* 2017, **8**, e2990.
56. Berger MD, Lenz HJ. The safety of monoclonal antibodies for treatment of colorectal cancer. *Expert Opin Drug Saf* 2016, **15**, 799-808.

57. An MM, Zou Z, Shen H, Liu P, Chen ML, Cao YB et al. Incidence and risk of significantly raised blood pressure in cancer patients treated with bevacizumab: An updated meta-analysis. *Eur J Clin Pharmacol* 2010, **66**, 813-821.
58. Schneider BP, Li L, Radovich M, Shen F, Miller KD, Flockhart DA et al. Genome-Wide Association Studies for Taxane-Induced Peripheral Neuropathy in ECOG-5103 and ECOG-1199. *Clin Cancer Res* 2015, **21**, 5082-5091.
59. Han JY, Shin ES, Lee YS, Ghang HY, Kim SY, Hwang JA et al. A genome-wide association study for irinotecan-related severe toxicities in patients with advanced non-small-cell lung cancer. *Pharmacogenomics J* 2013, **13**, 417-422.
60. Tesařová P, Tesař V. Proteinuria and hypertension in patients treated with inhibitors of the VEGF signalling pathway--incidence, mechanisms and management. *Folia Biol (Praha)* 2013, **59**, 15-25.
61. DJ et al. Genetic Variants of VEGFA and FLT4 Are Determinants of Survival in Renal Cell Carcinoma Patients Treated with Sorafenib. *Cancer Res* 2019, **79**, 231-41.
62. GTEx Consortium. The Genotype-Tissue Expression (GTEx) pilot analysis: Multitissue gene regulation in humans. *Science* 2015, **8**, 648-60.
63. Machiela MJ et al. LDlink: A web-based application for exploring population-specific haplotype structure and linking correlated alleles of possible functional variants. *Bioinformatics* 2015, **31**, 3555-7.
64. Angiogenesis Inhibitor. https://www.wikiwand.com/en/Angiogenesis_inhibitor. Accessed on August 7 (2019).
65. James Kent W et al. The human genome browser at UCSC. *Genome Res* 2002, **12**, 996-1006.
66. Blattler A et al. Cross-talk between site-specific transcription factors and DNA methylation states. *J Biol Chem* 2013 **288**, 34287-94.
67. Mir O, Coriat R, Cabanes L et al. An Observational Study of Bevacizumab-Induced Hypertension as a Clinical Biomarker of Antitumor Activity. *Oncologist* 2011; **16**: 1325-1332.
68. Hertz DL, Owzar K, Lessans S et al. Pharmacogenetic discovery in CALGB (alliance) 90401 and mechanistic validation of a VAC14 polymorphism that increases risk of docetaxel-induced neuropathy. *Clin Cancer Res* 2016; **22**: 4890-4900.
69. Thul PJ, Akesson L, Wiking M et al. A subcellular map of the human proteome. *Science* 2017; **356**: pii:eaal3321.

70. González C, Baez-Nieto D, Valencia I et al. K⁺ channels: Function-structural overview. *Compr Physiol* 2012; 2: 2087-2149.
71. Tipparaju SM, Liu SQ, Barski OA et al. NADPH binding to β -subunit regulates inactivation of voltage-gated K⁺ channels. *Biochem Biophys Res Commun* 2007; 359: 267-276.
72. Sobey CG. Potassium channel function in vascular disease. *Arterioscler Thromb Vasc Biol* 2001; 21: 28-38.
73. Martens JR, Gelband CH. Alterations in rat interlobar artery membrane potential and K⁺ channels in genetic and nongenetic hypertension. *Circ Res* 1996; 79: 295-301.
74. Banerjee B, Peiris DN, Koo SH et al. Genomic imbalances in key ion channel genes and telomere shortening in sudden cardiac death victims. *Cytogenet Genome Res* 2009; 122: 350-355.
75. Tur J, Chapalamadugu KC, Padawer T et al. Deletion of Kv β 1.1 subunit leads to electrical and haemodynamic changes causing cardiac hypertrophy in female murine hearts. *Exp Physiol* 2016; 101: 494-508.
76. Kulakovskiy IV, Vorontsov IE, Yevshin IS et al. HOCOMOCO: Towards a complete collection of transcription factor binding models for human and mouse via large-scale ChIP-Seq analysis. *Nucleic Acids Res* 2018; 46: D252-D259.
77. Niu Z, Li A, Zhang SX et al. Serum response factor micromanaging cardiogenesis. *Curr Opin Cell Biol* 2007; 19: 618-627.
78. Rouillard AD, Gundersen GW, Fernandez NF et al. The harmonizome: a collection of processed datasets gathered to serve and mine knowledge about genes and proteins. *Database (Oxford)* 2016; pii: baw100.
79. Sherry ST, Ward MH, Kholodov M et al. dbSNP: the NCBI database of genetic variation. *Nucleic Acids Res* 2001; 29: 308-311.
80. Reddish FN, Miller CL, Gorkhali R et al. Calcium dynamics mediated by the endoplasmic/sarcoplasmic reticulum and related diseases. *Int J Mol Sci* 2017; pii: E1024.
81. West AG, Gaszner M, Felsenfeld G. Insulators: Many functions, many mechanisms. *Genes Dev* 2002; 16: 271-288.
82. Brahmer JR, Dahlberg SE, Gray RJ et al. Sex differences in outcome with bevacizumab therapy: Analysis of patients with advanced-stage non-small cell lung cancer treated with or without bevacizumab in combination with paclitaxel and carboplatin in the eastern cooperative oncology group trial 459. *J Thorac Oncol* 2011; 6: 1031-08.

83. Li M, Mulkey F, Jiang C et al. Identification of a genomic region between SLC29A1 and HsP90AB1 associated with risk of bevacizumab-induced hypertension: CALGB 80405 (Alliance). *Clin Cancer Res* 2018; 24: 4734-4744
84. Wilhelm SM, Carter C, Tang LY, et al. BAY 43-9006 exhibits broad spectrum oral antitumor activity and targets the RAF/MEK/ERK pathway and receptor tyrosine kinases involved in tumor progression and angiogenesis. *Cancer Res* 2004;64:7099-109. <https://doi.org/10.1158/0008-5472.CAN-04-1443>.
85. Nexavar (Sorafenib).
<https://www.accessdata.fda.gov/drugsatfda_docs/label/2018/021923s020lbl.pdf>. Accessed 16 May 2020.
86. Costa LJ, Drabkin HA. Renal Cell Carcinoma: New Developments in Molecular Biology and Potential for Targeted Therapies. *Oncologist* 2007;12:1404-15. <https://doi.org/10.1634/theoncologist.12-12-1404>.
87. Li Y, Li S, Zhu Y, et al. Incidence and risk of sorafenib-induced hypertension: A systematic review and meta-analysis. *J Clin Hypertens* 2014;16:177-85. <https://doi.org/10.1111/jch.12273>.
88. Qi WX, Lin F, Sun YJ, et al. Incidence and risk of hypertension with pazopanib in patients with cancer: A meta-analysis. *Cancer Chemother Pharmacol* 2013;71:431-9. <https://doi.org/10.1007/s00280-012-2025-5>.
89. Zhu X, Stergiopoulos K, Wu S. Risk of hypertension and renal dysfunction with an angiogenesis inhibitor sunitinib: Systematic review and meta-analysis. *Acta Oncol (Madr)* 2009;8:9-17. <https://doi.org/10.1080/02841860802314720>.
90. Maitland ML, Kasza KE, Karrison T, et al. Ambulatory monitoring detects sorafenib-induced blood pressure elevations on the first day of treatment. *Clin Cancer Res* 2009;15:6250-7. <https://doi.org/10.1158/1078-0432.CCR-09-0058>.
91. Karar J, Maity A. PI3K/AKT/mTOR Pathway in Angiogenesis. *Front Mol Neurosci* 2011;4:51. <https://doi.org/10.3389/fnmol.2011.00051>.
92. Horowitz JR, Rivard A, Van Der Zee R, et al. Vascular endothelial growth factor/vascular permeability factor produces nitric oxide-dependent hypotension: Evidence for a maintenance role in quiescent adult endothelium. *Arterioscler Thromb Vasc Biol* 1997;17:2793-800. <https://doi.org/10.1161/01.ATV.17.11.2793>.
93. Rini BI. Quantifying hypertension in patients with cancer treated with sorafenib. *Lancet Oncol* 2008;9:86-7. [https://doi.org/10.1016/S1470-2045\(08\)70009-3](https://doi.org/10.1016/S1470-2045(08)70009-3).

94. Qin C, Cao Q, Li P, et al. The influence of genetic variants of sorafenib on clinical outcomes and toxic effects in patients with advanced renal cell carcinoma. *Sci Rep* 2016;6:20089. <https://doi.org/10.1038/srep20089>.
95. Robinson ES, Khankin EV, Karumanchi SA, et al. Hypertension induced by vascular endothelial growth factor signaling pathway inhibition: Mechanisms and potential use as a biomarker. *Semin Nephrol* 2010;30:591-601. <https://doi.org/10.1016/j.semnephrol.2010.09.007>.
96. Escudier B, Eisen T, Stadler WM, et al. Sorafenib in advanced clear-cell renal-cell carcinoma. *N Engl J Med* 2007;356:125-34. <https://doi.org/10.1056/NEJMoa060655>.
97. Crona DJ, Skol AD, Leppanen VM, et al. Genetic variants of VEGFA and FLT4 are determinants of survival in renal cell carcinoma patients treated with sorafenib. *Cancer Res* 2019;79:231-41. <https://doi.org/10.1158/0008-5472.CAN-18-1089>.
98. Quintanilha JCF, Wang J, Sibley AB et al. Bevacizumab-induced hypertension and proteinuria: A genome-wide analysis of more than 1,000 patients. Submitted to *J Natl Cancer Inst*.
99. Baldwin RM, Owzar K, Zembutsu H, et al. A genome-wide association study identifies novel loci for paclitaxel-induced sensory peripheral neuropathy in CALGB 40101. *Clin Cancer Res* 2012;18:5099-109. <https://doi.org/10.1158/1078-0432.CCR-12-1590>.
100. Dayem Ullah AZ, Oscanoa J, Wang J, et al. SNPnexus: Assessing the functional relevance of genetic variation to facilitate the promise of precision medicine. *Nucleic Acids Res* 2018;46:W109-W113. <https://doi.org/10.1093/nar/gky399>.
101. Ardlie KG, DeLuca DS, Segrè A V., Sullivan TJ, Young TR, Gelfand ET, et al. The Genotype-Tissue Expression (GTEx) pilot analysis: Multitissue gene regulation in humans. *Science* 2015;8:648-60. <https://doi.org/10.1126/science.1262110>.
102. Zuo C, Shin S, Keleş S. AtSNP: Transcription factor binding affinity testing for regulatory SNP detection. *Bioinformatics* 2015;31:3353-5. <https://doi.org/10.1093/bioinformatics/btv328>.
103. Zhong H, Chiles K, Feldser D, et al. Modulation of hypoxia-inducible factor 1 α expression by the epidermal growth factor/phosphatidylinositol 3-kinase/PTEN/AKT/FRAP pathway in human prostate cancer cells: Implications for tumor angiogenesis and therapeutics. *Cancer Res* 2000;60:1541-1545.
104. Forsythe JA, Jiang BH, Iyer NV, et al. Activation of vascular endothelial growth factor gene transcription by hypoxia-inducible factor 1. *Mol Cell Biol* 1996;16:4604-4613. <https://doi.org/10.1128/mcb.16.9.4604>.

105. Shymanets A, Prajwal, Bucher K, et al. P87 and p101 subunits are distinct regulators determining class I B phosphoinositide 3-kinase (PI3K) specificity. *J Biol Chem* 2013;288:31059-68. <https://doi.org/10.1074/jbc.M113.508234>.
106. Serban D, Leng J, Cheres D. H-ras regulates angiogenesis and vascular permeability by activation of distinct downstream effectors. *Circ Res* 2008;102:1350-8. <https://doi.org/10.1161/CIRCRESAHA.107.169664>.

WHAT IS CLAIMED IS:

1. A method comprising:
detecting a mutation in one or more nucleic acids in a sample obtained from a subject, wherein the subject is undergoing therapy or is a candidate for therapy with a VEGF-pathway inhibitor.
2. The method of claim 1, further comprising determining the risk of developing one or more VEGF-pathway inhibitor-induced toxicities in the subject based upon the presence or absence of the mutation in the one or more nucleic acids in the sample.
3. A method of predicting the risk of developing one or more VEGF-pathway inhibitor-induced toxicities in a subject, comprising:
 - a. detecting a mutation in one or more nucleic acids in a sample obtained from the subject, wherein the subject is undergoing therapy or is a candidate for therapy with a VEGF-pathway inhibitor; and
 - b. determining the risk of developing one or more VEGF-pathway inhibitor-induced toxicities in the subject based upon the presence or absence of the mutation in the one or more nucleic acids in the sample.
4. The method of any one of claims 1-3, wherein detecting a mutation in one or more nucleic acids in the sample comprises detecting a single nucleotide polymorphism (SNP) in the one or more nucleic acids in the sample.
5. The method of claim 4, wherein the SNP is located in a gene provided in Table 8 or Table 9.
6. The method of claim 4, wherein the SNP is selected from the SNPs provided in Table 4, Table 5, Table 6, Table 7, Table 10, Table 11, Table 12, Table 13, rs444904, and rs427554.
7. The method of claim 4, wherein the SNP is selected from the group consisting of rs339947, rs12482855, rs13135230, rs2350620, rs11662763, rs6770663, rs408130, rs418173, rs12482855, rs444904, and rs427554.

8. The method of any one of claims 2-7, wherein the one or more VEGF-pathway inhibitor-induced toxicities are selected from proteinuria, hypertension, or both.
9. The method of claim 8, wherein determining the risk of developing one or more VEGF-pathway inhibitor-induced toxicities in the subject comprises:
 - a. diagnosing the subject as having a high risk of developing proteinuria when the base identified at rs339947 is an adenine, the base identified at rs12482855 is an adenine, the base identified at rs11662763 is an adenine, the base identified at rs408130 is an adenine, the base identified at rs418173 is an adenine, or the base identified at rs12482855 is an adenine;
 - b. diagnosing the subject as having a high risk of developing hypertension when the base identified at rs13135230 is an adenine, the base identified at rs11662763 is an adenine, the base identified at rs6770663 is a guanine, the base identified at rs444904 is an adenine, or the base identified at rs427554 is an adenine;
 - c. diagnosing the subject as having a low risk of developing hypertension when the base identified at rs2350620 is a guanine; or
 - d. diagnosing the subject as having a high risk of developing proteinuria and hypertension when the base identified at rs11662763 is an adenine.
10. The method of any one of claims 2-9, further comprising lowering the dose of the VEGF-pathway inhibitor or ceasing treatment with the VEGF-pathway inhibitor when the subject is determined to have a high risk of developing proteinuria, hypertension, or both.
11. The method of any one of claims 2-10, further comprising providing the subject with one or more supportive therapies when the subject is determined to have a high risk of developing proteinuria, hypertension, or both, wherein the one or more supportive therapies include one or more anti-hypertensive agents, one or more proteinuria medications, or a combination thereof.
12. The method of one of claims 2-9, further comprising providing the subject with a VEGF-pathway inhibitor when the subject is determined to have a low risk of developing proteinuria, hypertension, or both.

13. A method of treating a subject, the method comprising the steps of:
 - a. detecting a mutation in one or more nucleic acids in a sample obtained from a subject, wherein the subject is undergoing therapy or is a candidate for therapy with a VEGF-pathway inhibitor;
 - b. determining the risk of developing one or more VEGF-pathway inhibitor-induced toxicities in the subject based upon the presence or absence of the mutation in the one or more nucleic acids in the sample; and
 - c. modulating therapy with a VEGF-pathway inhibitor and/or providing the subject with one or more supportive therapies based upon the determined risk of developing one or more VEGF-pathway inhibitor-induced toxicities in the subject.
14. A method of treating a subject, the method comprising the steps of:
 - a. determining the risk of developing one or more VEGF-pathway inhibitor-induced toxicities in the subject based upon the presence or absence of a mutation in one or more nucleic acids in a sample obtained from a subject, wherein the subject is undergoing therapy or is a candidate for therapy with a VEGF-pathway inhibitor; and
 - b. modulating therapy with a VEGF-pathway inhibitor and/or providing the subject with one or more supportive therapies based upon the determined risk of developing one or more VEGF-pathway inhibitor-induced toxicities in the subject.
15. The method of any claim 13 or 14, wherein detecting a mutation in one or more nucleic acids in the sample comprises detecting a single nucleotide polymorphism (SNP) in the one or more nucleic acids in the sample.
16. The method of claim 15, wherein the SNP is located in a gene provided in Table 8 or Table 9.
17. The method of claim 15, wherein the SNP is selected from the SNPs provided in Table 4, Table 5, Table 6, Table 7, Table 10, Table 11, Table 12, Table 13, rs444904, and rs427554.

18. The method of claim 15, wherein the SNP is selected from the group consisting of rs339947, rs12482855, rs13135230, rs2350620, rs11662763, rs6770663, rs408130, rs418173, rs12482855, rs444904, and rs427554.
19. The method of any one of claims 13-18, wherein the one or more VEGF-pathway inhibitor-induced toxicities are selected from proteinuria, hypertension, or both.
20. The method of claim 19, wherein determining the risk of developing one or more VEGF-pathway inhibitor-induced toxicities in the subject comprises:
 - a. diagnosing the subject as having a high risk of developing proteinuria when the base identified at rs339947 is an adenine, the base identified at rs12482855 is an adenine, the base identified at rs11662763 is an adenine, the base identified at rs408130 is an adenine, the base identified at rs418173 is an adenine, or the base identified at rs12482855 is an adenine;
 - b. diagnosing the subject as having a high risk of developing hypertension when the base identified at rs13135230 is an adenine, the base identified at rs11662763 is an adenine, the base identified at rs6770663 is a guanine, the base identified at rs444904 is an adenine, or the base identified at rs427554 is an adenine;
 - c. diagnosing the subject as having a low risk of developing hypertension when the base identified at rs2350620 is a guanine; or
 - d. diagnosing the subject as having a high risk of developing proteinuria and hypertension when the base identified at rs11662763 is an adenine.
21. The method of claim 20, comprising:
 - a. lowering the dose of the VEGF-pathway inhibitor or ceasing treatment with the VEGF-pathway inhibitor when the subject is determined to have a high risk of developing proteinuria, hypertension, or both; or
 - b. providing the subject with a VEGF-pathway inhibitor when the subject is determined to have a low risk of developing proteinuria, hypertension, or both.

22. The method of claim 20 or 21, comprising providing the subject with one or more supportive therapies when the subject is determined to have a high risk of developing proteinuria, hypertension, or both, wherein the one or more supportive therapies include one or more anti-hypertensive agents, one or more proteinuria medications, or a combination thereof.
23. The method of any one of claims 13-22, wherein the subject was receiving a first supportive therapy prior to administration of the VEGF-pathway inhibitor, and wherein providing the subject with one or more supportive therapies comprises adding a second supportive therapy to the subject's treatment regimen, increasing the dose of the first supportive therapy, switching the subject to a different supportive therapy relative to the first supportive therapy, and/or switching the subject to a supportive therapy that is in a different class of therapeutic agent relative to the first supportive therapy.
24. The method of any one of claims 13-23, wherein the supportive therapy comprises blood pressure monitoring.
25. The method of any one of claims 13-24, wherein at least one of the one or more supportive therapies is an anti-hypertensive agent of a class selected from the group consisting of diuretics, beta blockers, alpha and beta blockers, calcium channel blockers, Angiotensin-converting enzyme (ACE) inhibitors, angiotensin II receptor antagonists (ARBs), adrenergic receptor antagonists, vasodilators, renin inhibitors, aldosterone receptor antagonists, alpha-2 adrenergic receptor agonists, central alpha-2 agonists and other centrally acting drugs, and endothelin receptor blockers.
26. The method of any one of claims 13-25, wherein the modulating therapy with the VEGF pathway inhibitor comprises reducing exposure of the subject to the VEGF pathway inhibitor.
27. The method of claim any one of claims 13-25, wherein modulating therapy with the VEGF pathway inhibitor comprises delaying initiation of treatment with the VEGF inhibitor, reducing the dose of the VEGF inhibitor, reducing the total number of doses of the VEGF inhibitor, reducing the dosing frequency of the

- VEGF inhibitor, and/or selecting a different VEGF pathway inhibitor or a non-VEGF pathway inhibitor therapy in the method of treating the patient.
28. The method of claim 27, wherein reducing the dose or the total number of doses of the VEGF inhibitor comprises reducing the dose or the total number of doses by about 5%, about 10%, about 25%, about 33%, about 50%, or about 75% relative to a reference dose or a reference total number of doses, wherein the reference dose or the reference total number of doses are the dose or total number of doses provided in prescribing information for the VEGF inhibitor.
 29. The method of claim 27, wherein reducing the dosing frequency of the VEGF inhibitor comprises reducing the dosing frequency to about half as often as the dosing frequency provided in prescribing information for the VEGF inhibitor.
 30. The method of any one of claims 1-29, wherein the VEGF-pathway inhibitor is an antibody or a small molecule.
 31. The method of claim 30, wherein the VEGF-pathway inhibitor is selected from the group consisting of bevacizumab, bevacizumab-awwb, bevacizumab-bvzr, ranibizumab, aflibercept, ziv-aflibercept, lenalidomide, lenvatinib, ramucirumab, cabozantinib, pazopanib, sunitinib malate, regorafenib, axitinib, tipiracil and trifluridine, ponatinib, vandetanib, sorafenib, everolimus, thalidomide, temsirolimus, interferon alfa, interferon alfa-2B, interferon alfa-N3, peginterferon alfa-2B, peginterferon alfa-2A, rhEndostatin, cediranib, semaxanib, pomalidomide, alitretinoin, imiquimod, sinecatechins, vismodegib, sonidegib, pegaptanib sodium, dexamethasone intravitreal implant, fluocinolone acetonide, conbercept, brolocizumab-dbl, selpercatinib, nintedanib, apatinib, and motesanib.
 32. The method of any one of claims 1-31, wherein the subject is a mammal.
 33. The method of claim 32, wherein the subject is a human.
 34. A method for treating or preventing a VEGF pathway inhibitor-induced toxicity in a subject in need of treatment with a VEGF pathway inhibitor, the method comprising

- (i) identifying the subject as having a mutation in the gene *KCNAB1* and
 - (ii) treating the subject with one or more prophylactic therapies for the toxicity.
35. The method of claim 34, wherein the mutation in the gene is a mutation that lowers expression of *KCNAB1* relative to wildtype.
36. The method of claim 35, wherein the mutation is SNP rs6770663.
37. The method of claim 36, wherein the base identified at rs6770663 is a guanine.
38. The method of any one of claims 34-37, wherein the toxicity comprises hypertension.
39. The method of claim 38, wherein the prophylactic therapy is an anti-hypertensive agent.
40. The method of claim 39, wherein the anti-hypertensive agent is in a class of drug selected from the group consisting of loop diuretics, thiazide diuretics, thiazide-like diuretics, potassium-sparing diuretics, calcium channel blockers, ACE inhibitors, angiotensin II receptor antagonists, adrenergic receptor antagonists, vasodilators, renin inhibitors, aldosterone receptor antagonists, alpha-2 adrenergic receptor agonists, and endothelin receptor blockers.
41. The method of any one of claims 34-40, further comprising reducing exposure of the subject to the VEGF pathway inhibitor relative to the exposure of a subject who is treated as provided on prescribing information for the VEGF pathway inhibitor.
42. The method of claim 41, wherein reducing the exposure of the subject to the VEGF pathway inhibitor comprises delaying initiation of treatment with the VEGF inhibitor, reducing the dose of the VEGF inhibitor, reducing the total number of doses of the VEGF inhibitor, reducing the dosing frequency of the VEGF inhibitor, and/or selecting a different VEGF pathway inhibitor or a non-VEGF pathway inhibitor therapy in the method of treating the patient.

43. The method of claim 41, wherein reducing the dose or the total number of doses of the VEGF inhibitor comprises reducing the dose or the total number of doses by about 5%, about 10%, about 25%, about 33%, about 50%, or about 75% relative to a reference dose or a reference total number of doses, wherein the reference dose or the reference total number of doses are the dose or total number of doses provided in prescribing information for the VEGF inhibitor.
44. The method of claim 41, wherein reducing the dosing frequency of the VEGF inhibitor comprises reducing the dosing frequency to about half as often as the dosing frequency provided in prescribing information for the VEGF inhibitor.
45. The method of any one of claims 34-44, wherein the subject is treated with the prophylactic therapy prior to or concurrently with the VEGF pathway inhibitor.
46. The method of any one of claims 34-45, wherein treatment of the subject with the VEGF pathway inhibitor is delayed until the subject has been treated with the prophylactic therapy for at least 1 day.
47. The method of claim any one of claims 34-46, wherein identifying the subject as having a mutation in *KCNAB1* comprises obtaining a biological sample from the subject and testing the subject for the presence or absence of the mutation.
48. The method of any one of claims 34-47, wherein the VEGF pathway inhibitor is selected from the group consisting of bevacizumab, bevacizumab-awwb, bevacizumab bvzr, ranibizumab, aflibercept, ziv-aflibercept, lenalidomide, lenvatinib, ramucirumab, cabozantinib, pazopanib, sunitinib malate, regorafenib, axitinib, tipiracil and trifluridine, ponatinib, vandetanib, sorafenib, everolimus, thalidomide, temsirolimus, interferon alfa, interferon alfa-2B, interferon alfa-N3, peginterferon alfa-2B, peginterferon alfa-2A, rhEndostatin, cediranib, semaxanib, pomalidomide, alitretinoin, imiquimod, sinecatechins, vismodegib, sonidegib, pegaptanib sodium, dexamethasone intravitreal implant, fluocinolone acetonide, conbercept, brotucizumab-dblb, selpercatinib, nintedanib, apatinib, and motesanib.
49. The method of claim 48, wherein the VEGF pathway inhibitor is bevacizumab.

50. The method of claim 49, wherein the method comprises identifying the presence of SNP rs6770663 in a biological sample obtained from the subject, modulating the treatment of the subject by administering an anti-hypertensive agent to the subject prior to or concurrently with administration of bevacizumab, monitoring the blood pressure of the subject, and/or modulating the dose of bevacizumab administered to the subject.
51. A method for treating a subject having a disease or disorder associated with neovascularization or angiogenesis, the method comprising
- (i) identifying the subject as having a mutation in the gene *KCNAB1*;
 - (ii) treating the subject with an anti-hypertensive agent; and
 - (iii) treating the subject with a VEGF pathway inhibitor.
52. The method of claim 51, wherein the mutation in the gene is a mutation that lowers expression of *KCNAB1* relative to wild type.
53. The method of claim 51 or 52, wherein the mutation is SNP rs6770663.
54. The method of any one of claims 51-53, wherein the anti-hypertensive agent is in a drug class selected from the group consisting of loop diuretics, thiazide diuretics, thiazide-like diuretics, potassium-sparing diuretics, calcium channel blockers, ACE inhibitors, angiotensin II receptor antagonists, adrenergic receptor antagonists, vasodilators, renin inhibitors, aldosterone receptor antagonists, alpha-2 adrenergic receptor agonists, and endothelin receptor blockers.
55. The method of any one of claims 51-54, further comprising monitoring the blood pressure of the subject.
56. The method of claim any one of claims 51-55, wherein treating the subject with an anti-hypertensive agent comprises adding one or more additional anti-hypertensive agent to the subject's treatment regimen, switching the subject's anti-hypertensive treatment regimen to a different anti-hypertensive agent, and/or increasing the dose and/or frequency of dosing of an anti-hypertensive

agent relative to the dose administered to the subject prior to treatment with the VEGF pathway inhibitor.

57. The method of any one of claims 51-56, wherein treating the subject with the VEGF pathway inhibitor comprises reducing exposure of the subject to the VEGF pathway inhibitor relative to the exposure of a subject treated as provided on prescribing information for the VEGF pathway inhibitor.
58. The method of claim 57, wherein reducing the exposure of the subject to the VEGF pathway inhibitor comprises delaying initiation of treatment with the VEGF inhibitor, reducing the dose of the VEGF inhibitor, reducing the total number of doses of the VEGF inhibitor, reducing the dosing frequency of the VEGF inhibitor, and/or selecting a different VEGF pathway inhibitor or a non-VEGF pathway inhibitor therapy in the method of treating the patient.
59. The method of claim 58, wherein reducing the dose or the total number of doses of the VEGF inhibitor comprises reducing the dose or the total number of doses by about 5%, about 10%, about 25%, about 33%, about 50%, or about 75% relative to a reference dose or a reference total number of doses, wherein the reference dose or the reference total number of doses are the dose or total number of doses provided in prescribing information for the VEGF inhibitor.
60. The method of claim 58, wherein reducing the dosing frequency of the VEGF inhibitor comprises reducing the dosing frequency to about half as often as the dosing frequency provided in prescribing information for the VEGF inhibitor.
61. The method of any one of claims 51-60, wherein identifying the subject as having a mutation in *KCNAB1* comprises obtaining a biological sample from the subject and testing the subject for the presence or absence of the mutation.
62. The method of claim 61, wherein the method comprises detecting the presence of a guanine at the base identified as rs6770663 in the biological sample.
63. The method of any one of claims 51-63, wherein the VEGF pathway inhibitor is selected from the group consisting of bevacizumab, bevacizumab-awwb, bevacizumab bvzr, ranibizumab, aflibercept, ziv-aflibercept, lenalidomide, lenvatinib, ramucirumab, cabozantinib, pazopanib, sunitinib malate,

regorafenib, axitinib, tipiracil and trifluridine, ponatinib, vandetanib, sorafenib, everolimus, thalidomide, temsirolimus, interferon alfa, interferon alfa-2B, interferon alfa-N3, peginterferon alfa-2B, peginterferon alfa-2A, rhEndostatin, cediranib, semaxanib, pomalidomide, alitretinoin, imiquimod, sinecatechins, vismodegib, sonidegib, pegaptanib sodium, dexamethasone intravitreal implant, fluocinolone acetonide, conbercept, brotuzumab-dbl, selipergatinib, nintedanib, apatinib, and motesanib.

64. The method of claim 63, wherein the VEGF pathway inhibitor is bevacizumab.

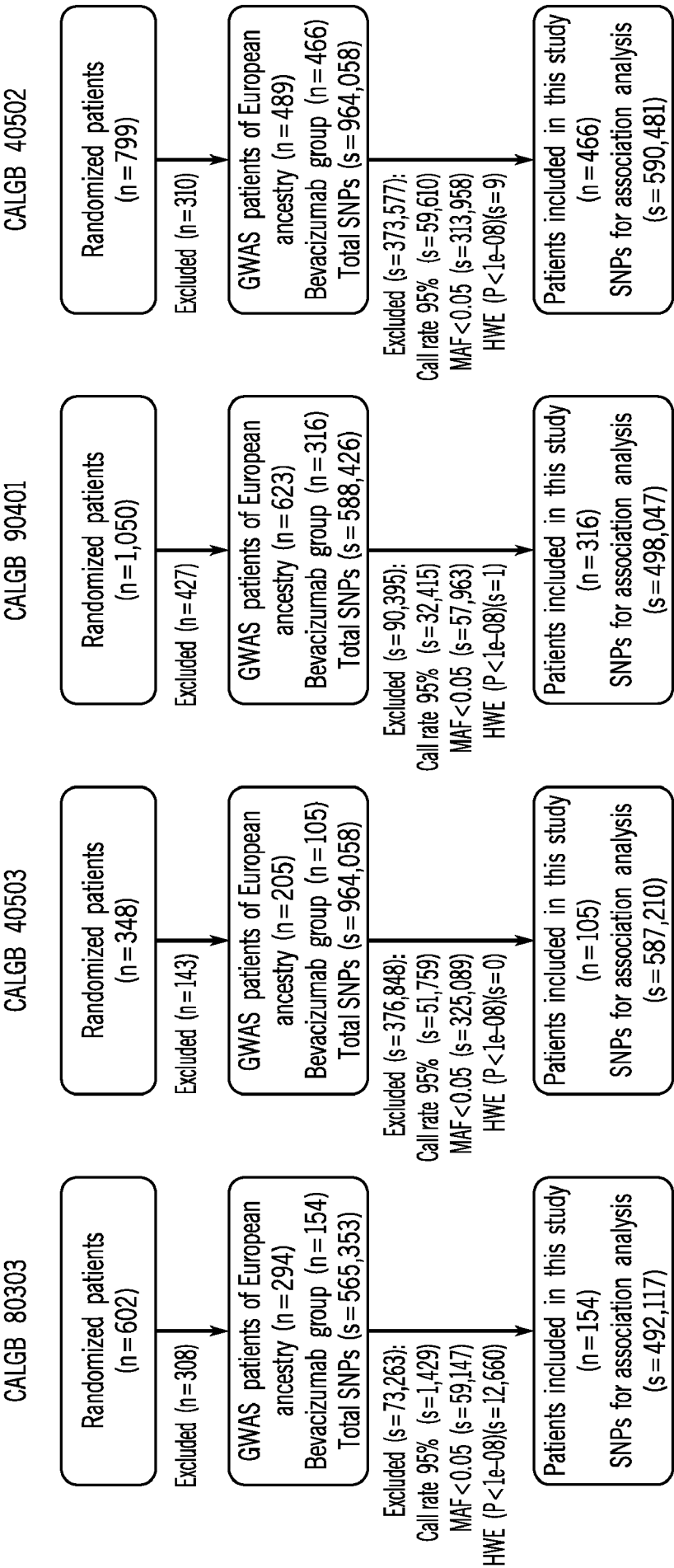


FIG. 1

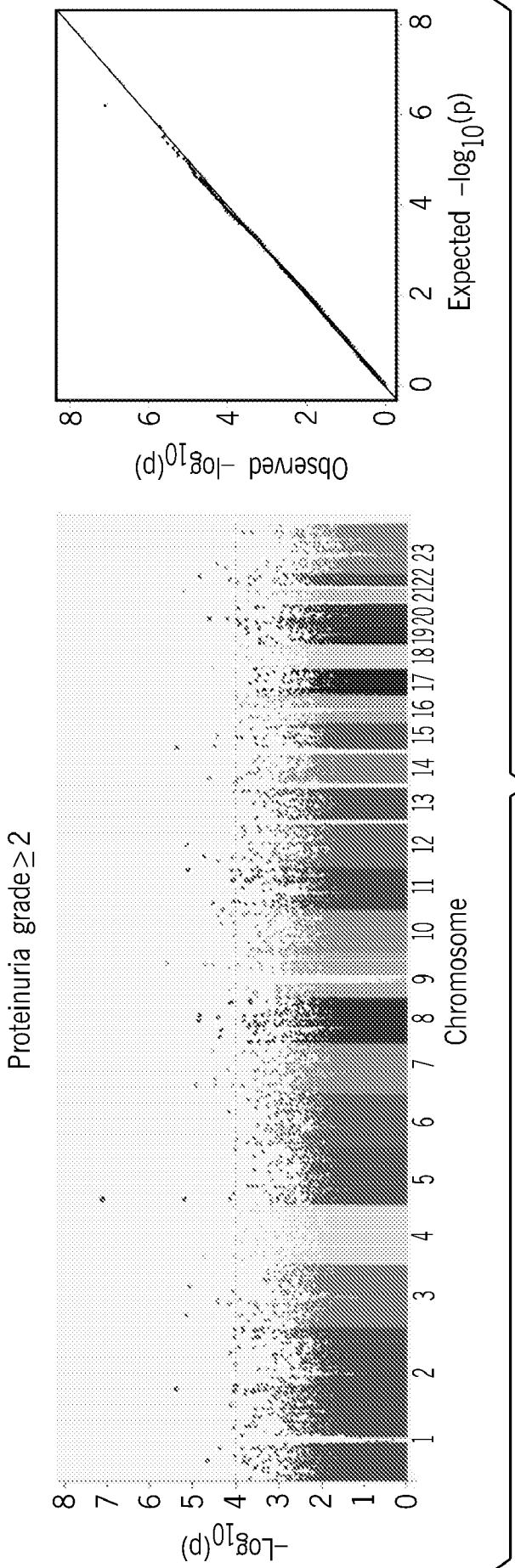


FIG. 2

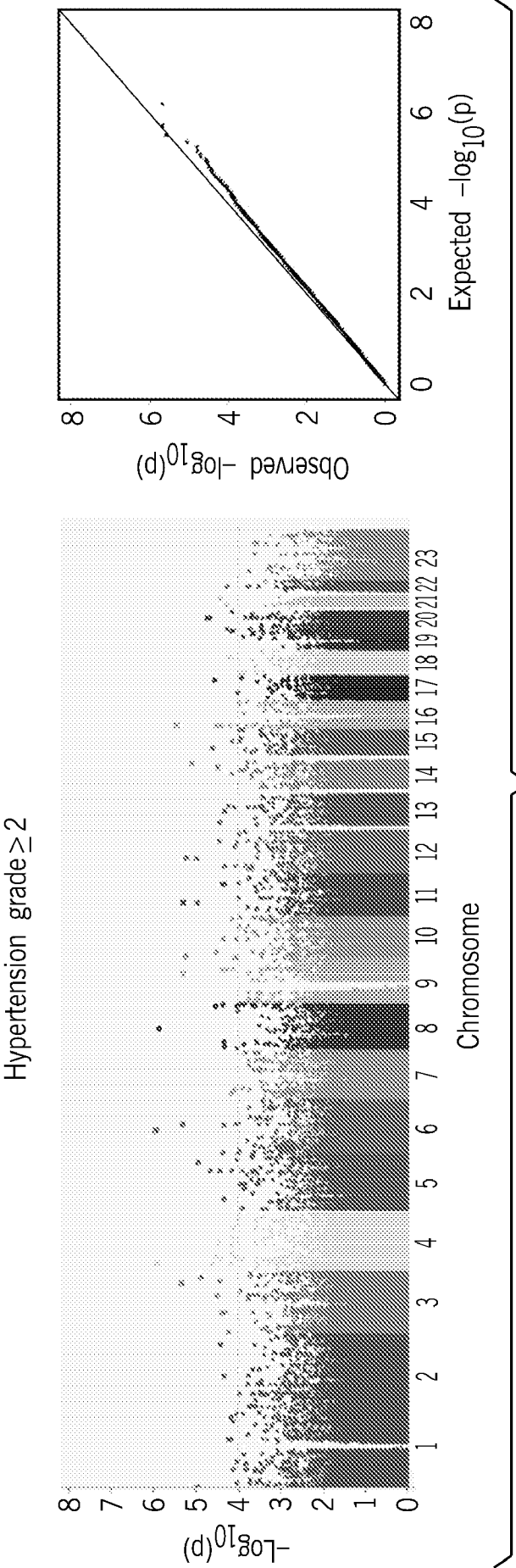


FIG. 2 (CONT.)

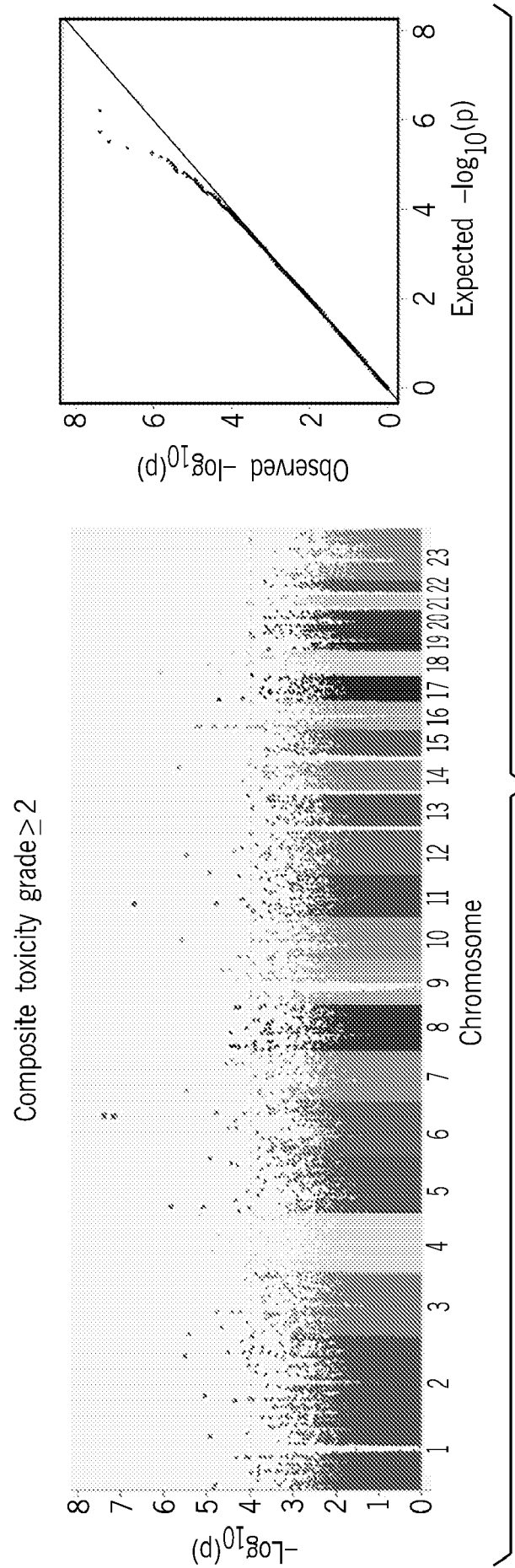


FIG. 2 (CONT.)

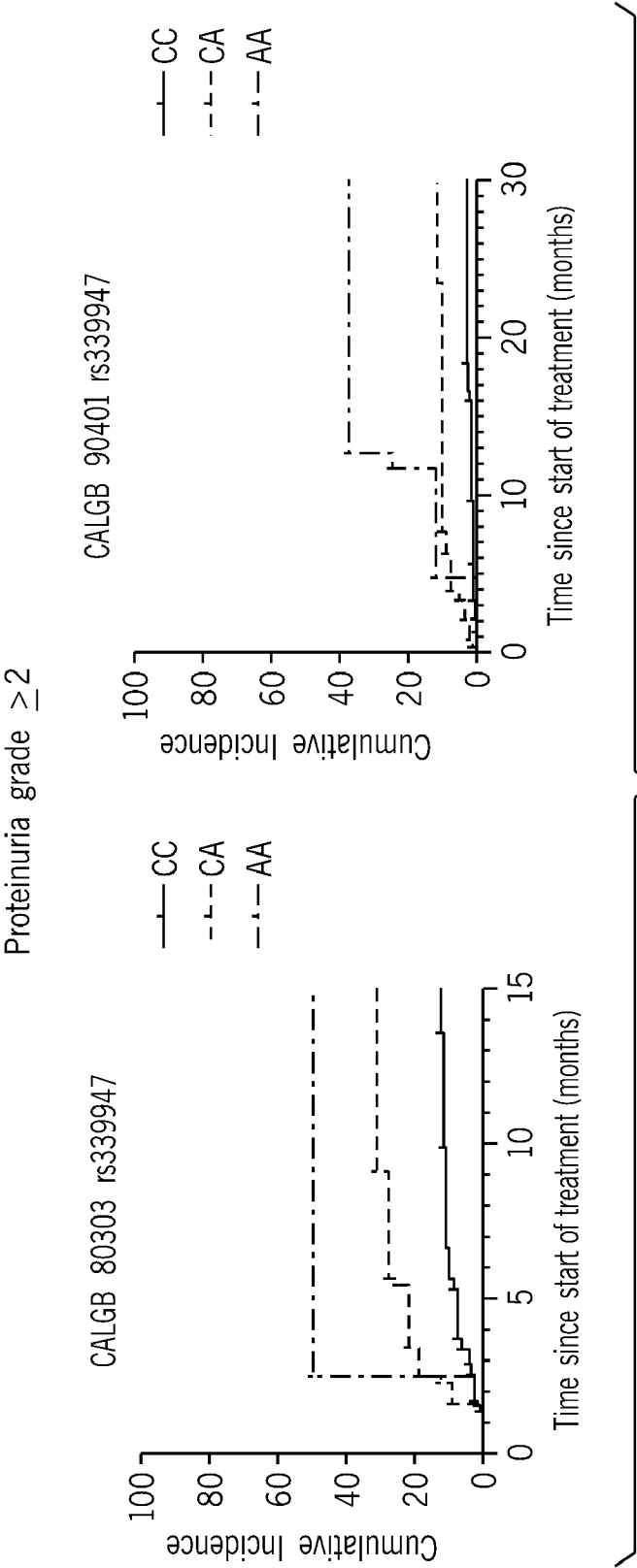


FIG. 3

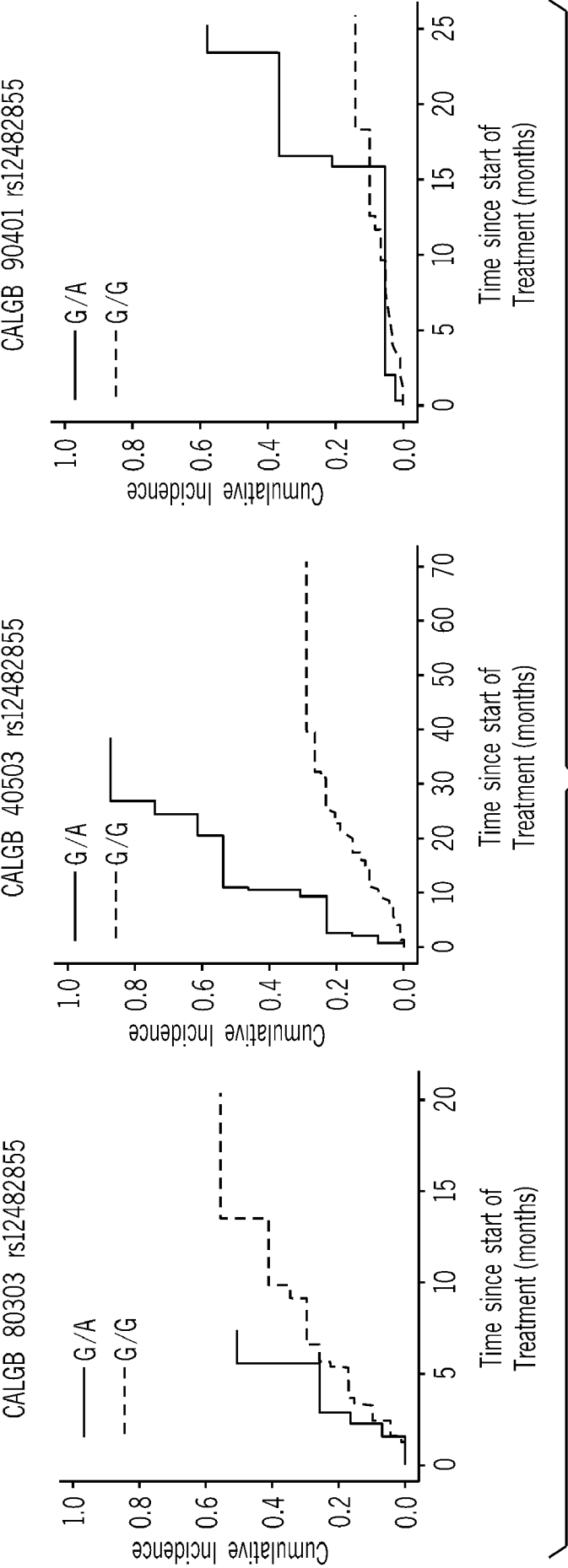


FIG. 3 (CONT.)

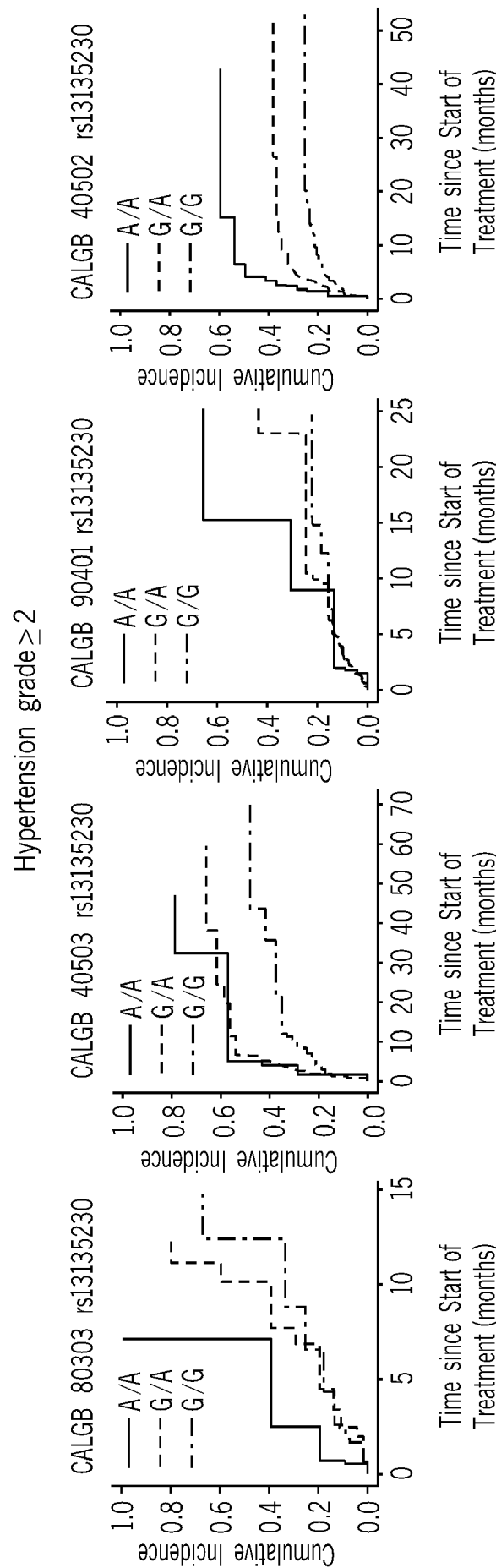


FIG. 3 (CONT.)

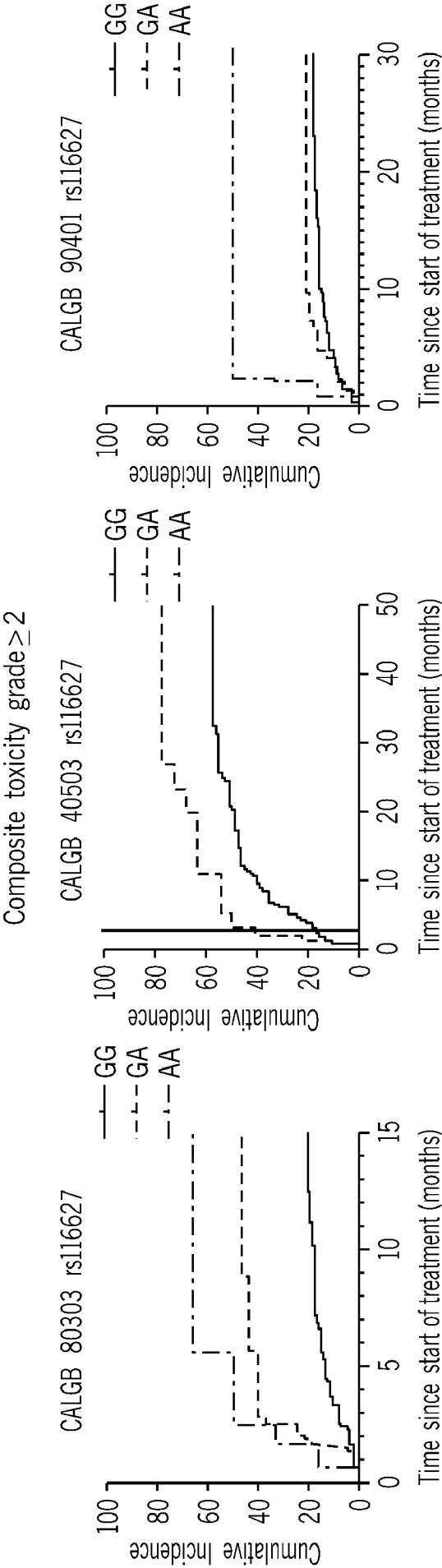


FIG. 3 (CONT.)

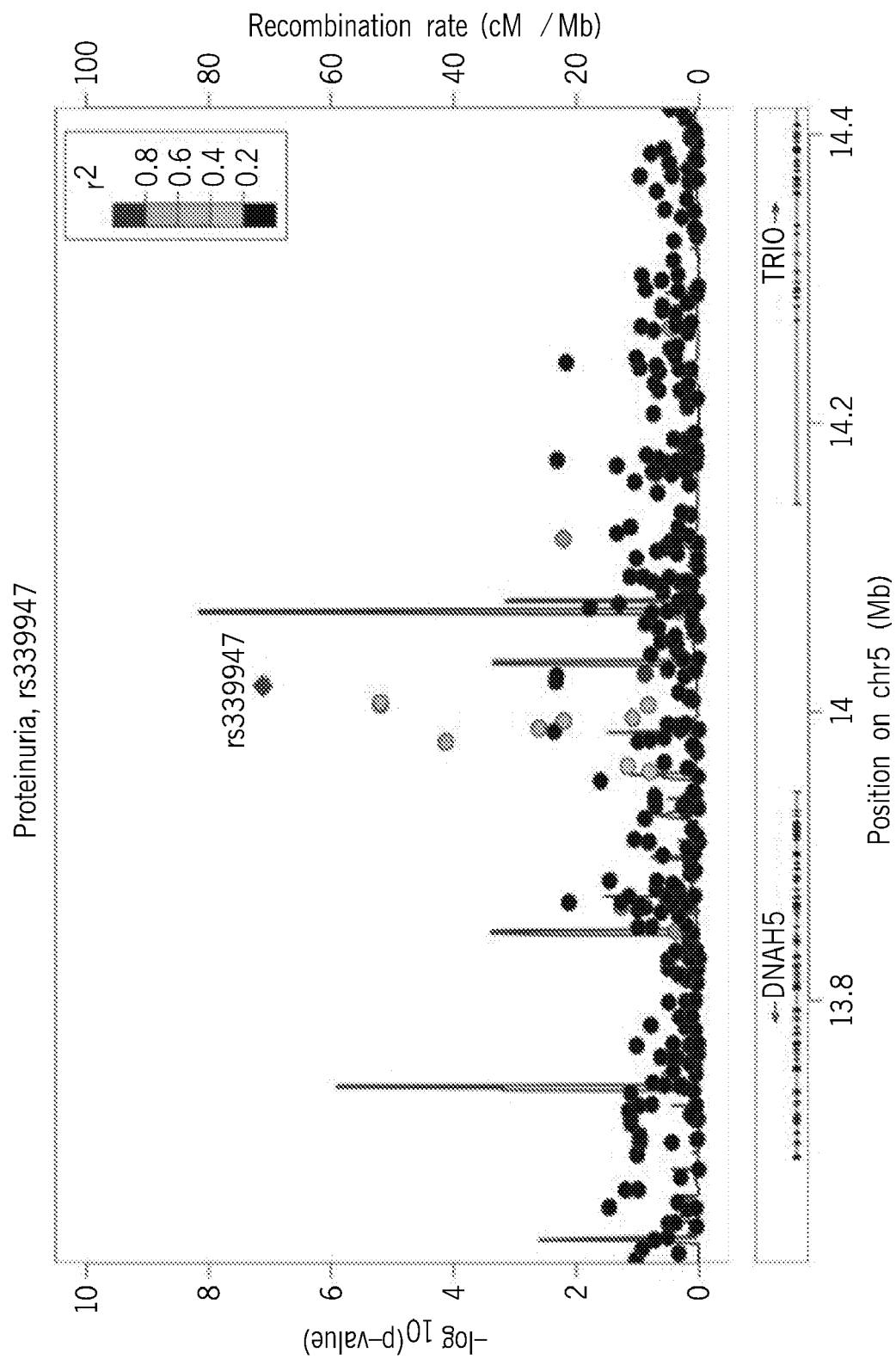


FIG. 4A

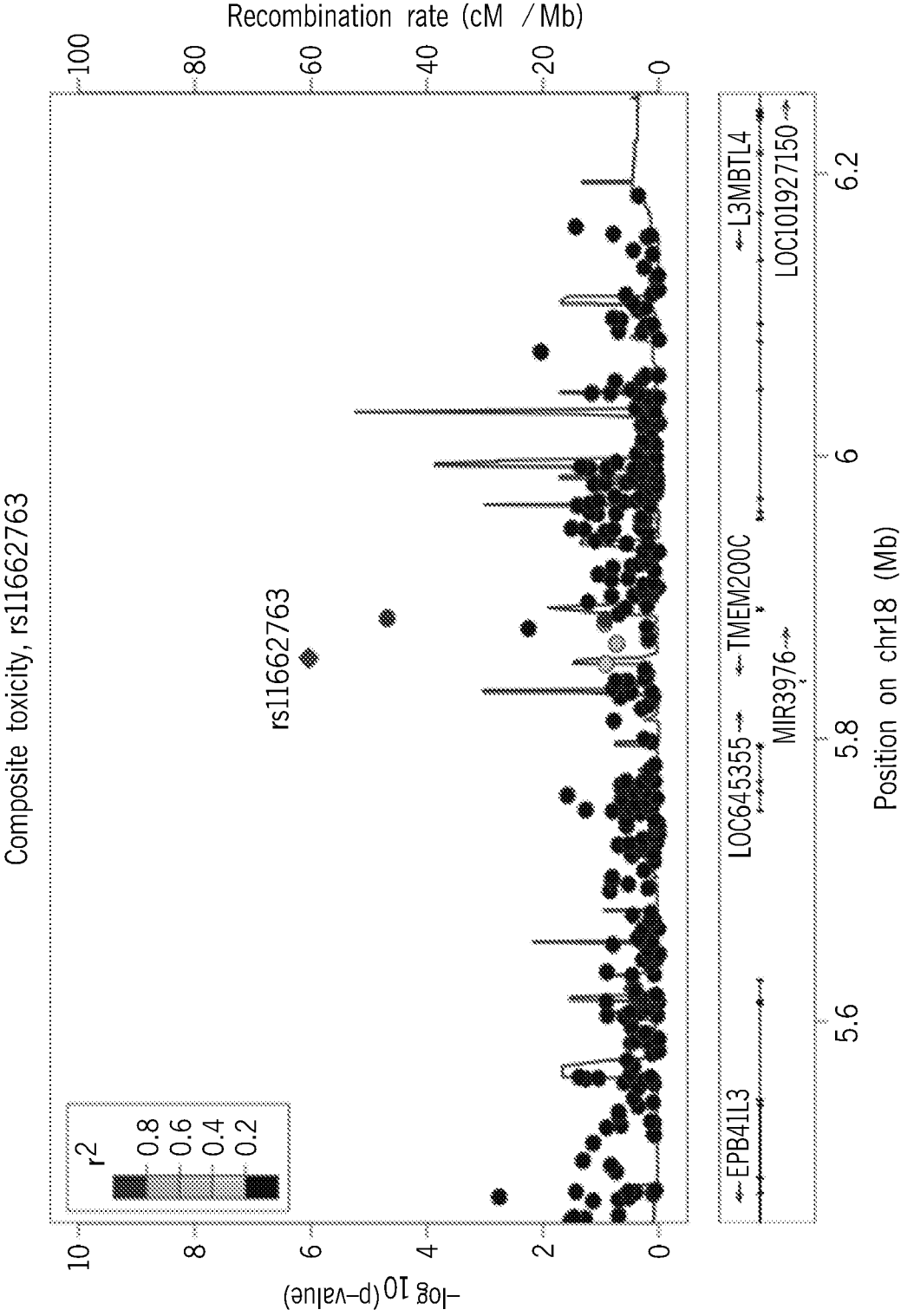


FIG. 4A (CONT.)

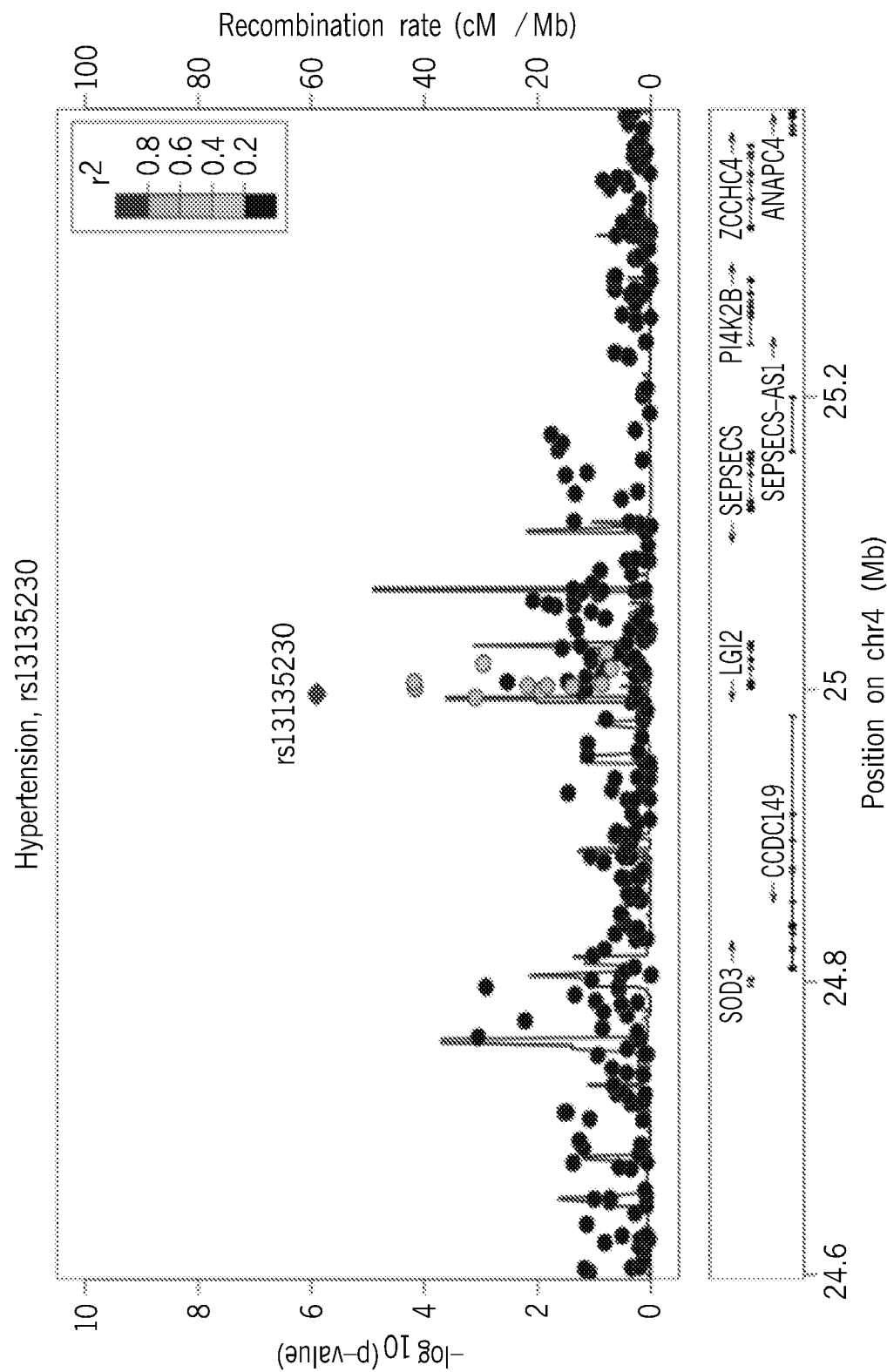


FIG. 4B

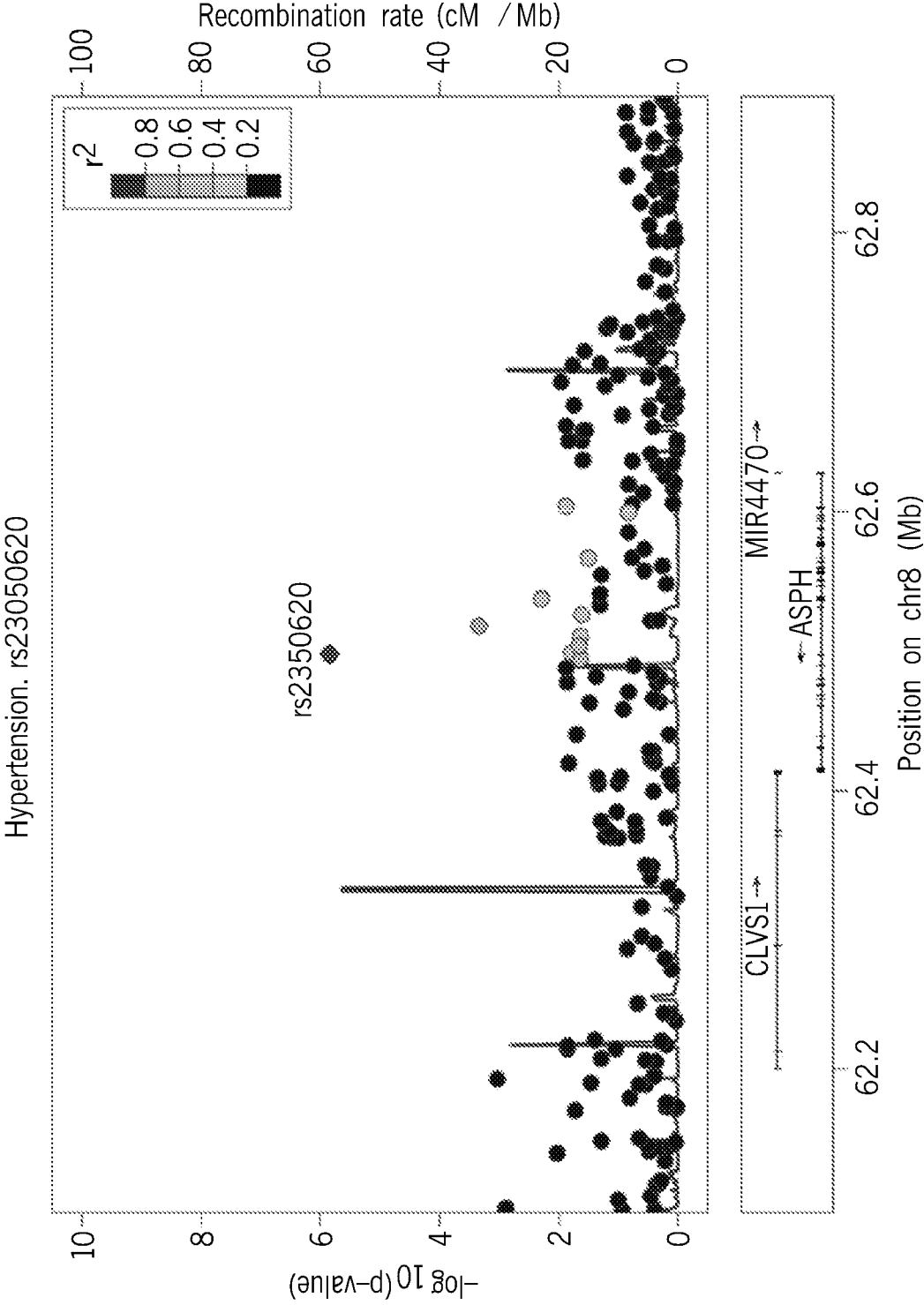


FIG. 4B (CONT.)

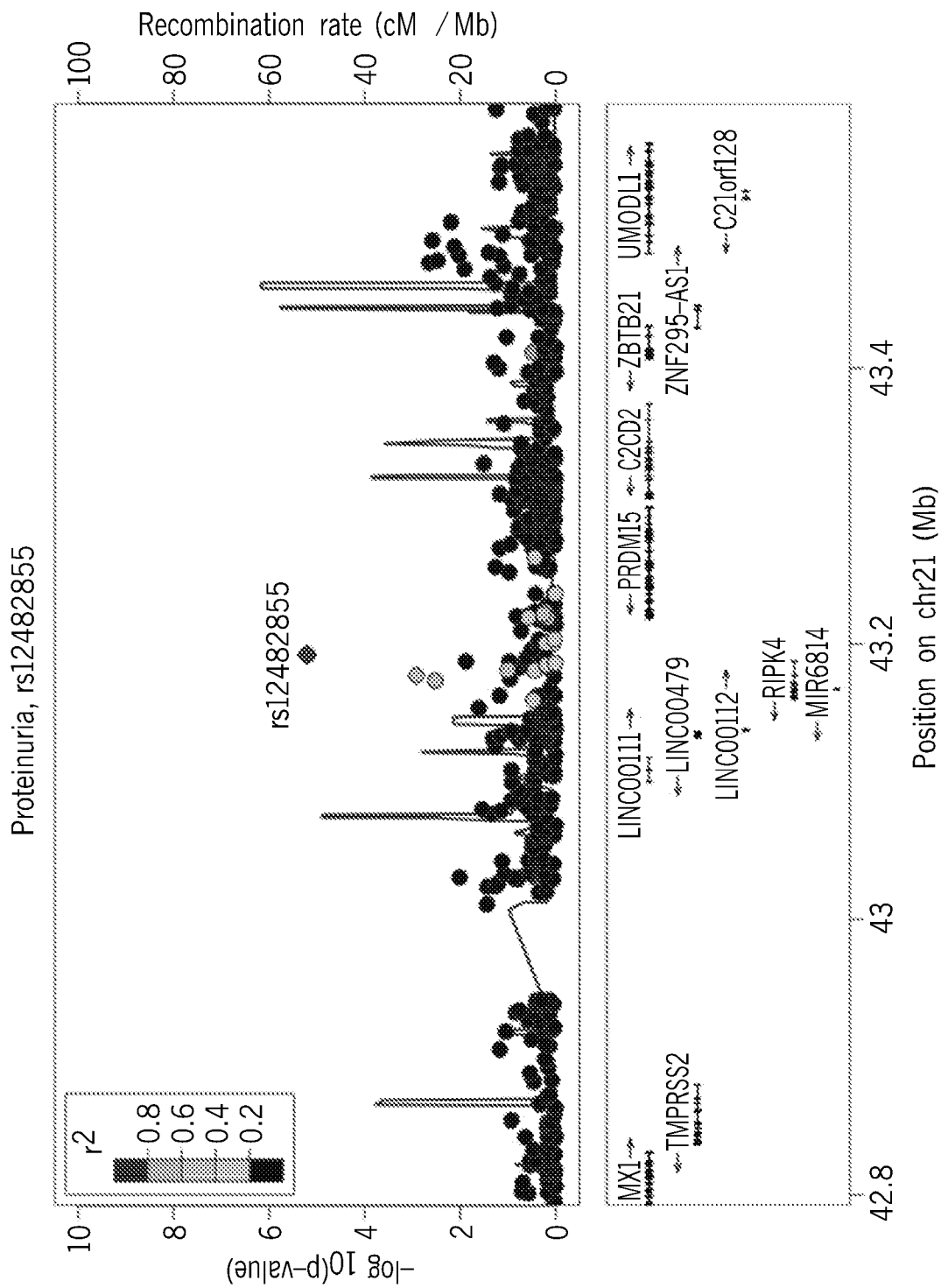


FIG. 4C

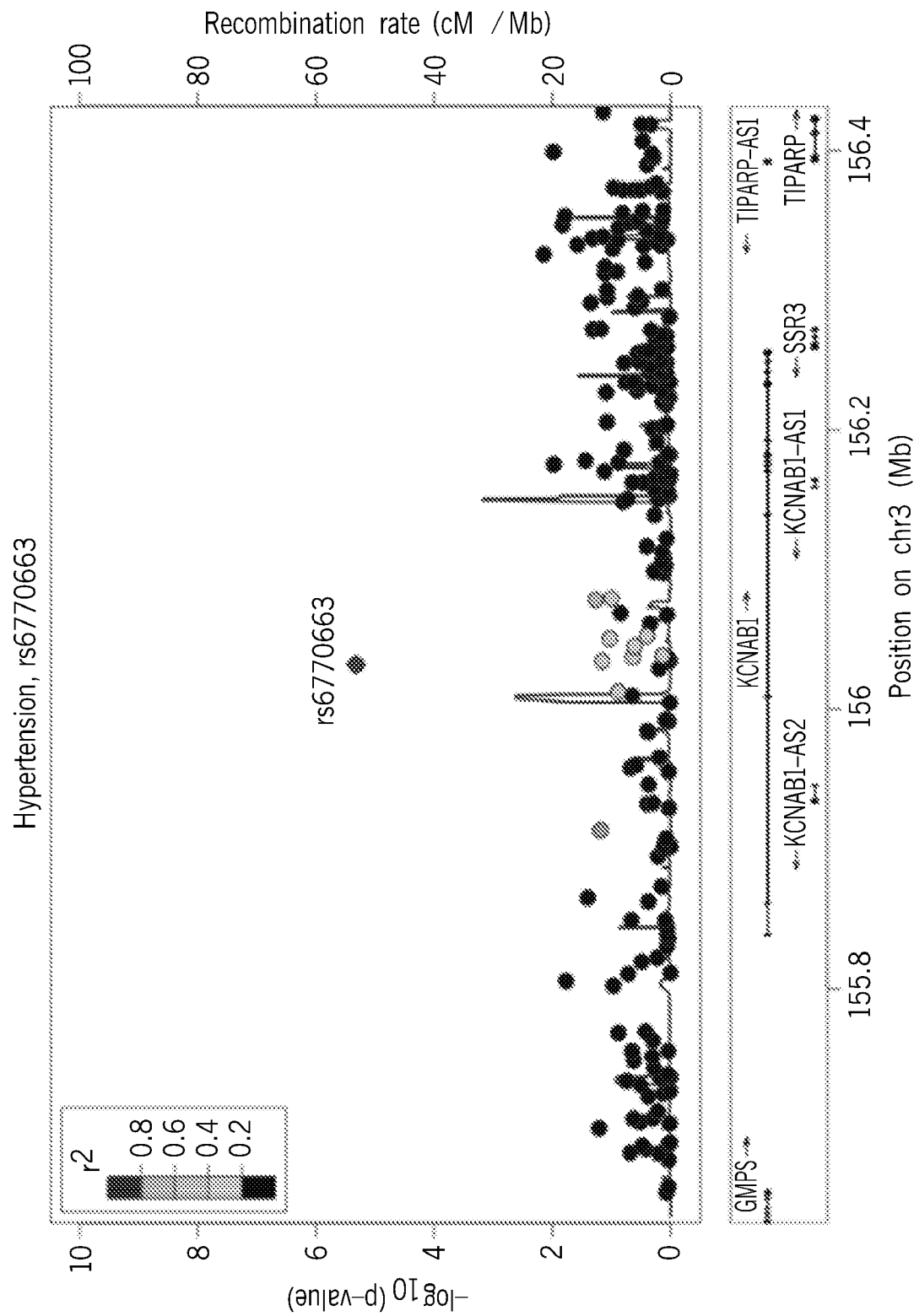


FIG. 4C (CONT.)

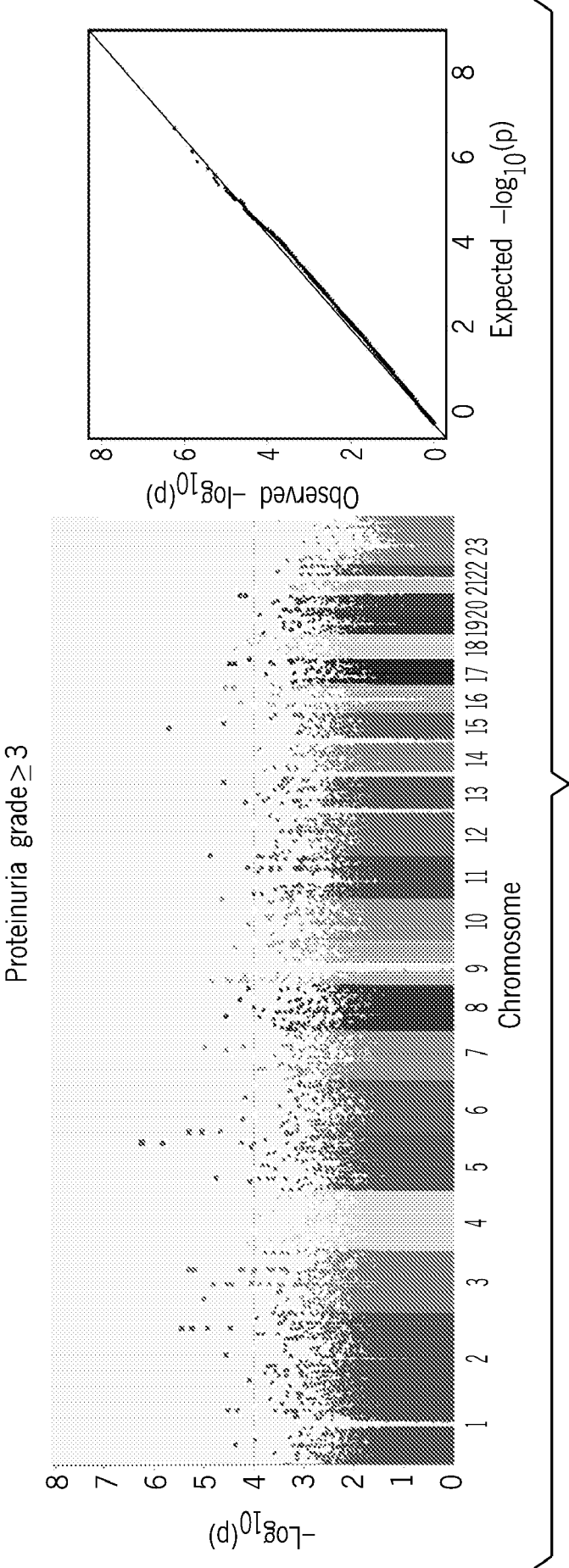


FIG. 5

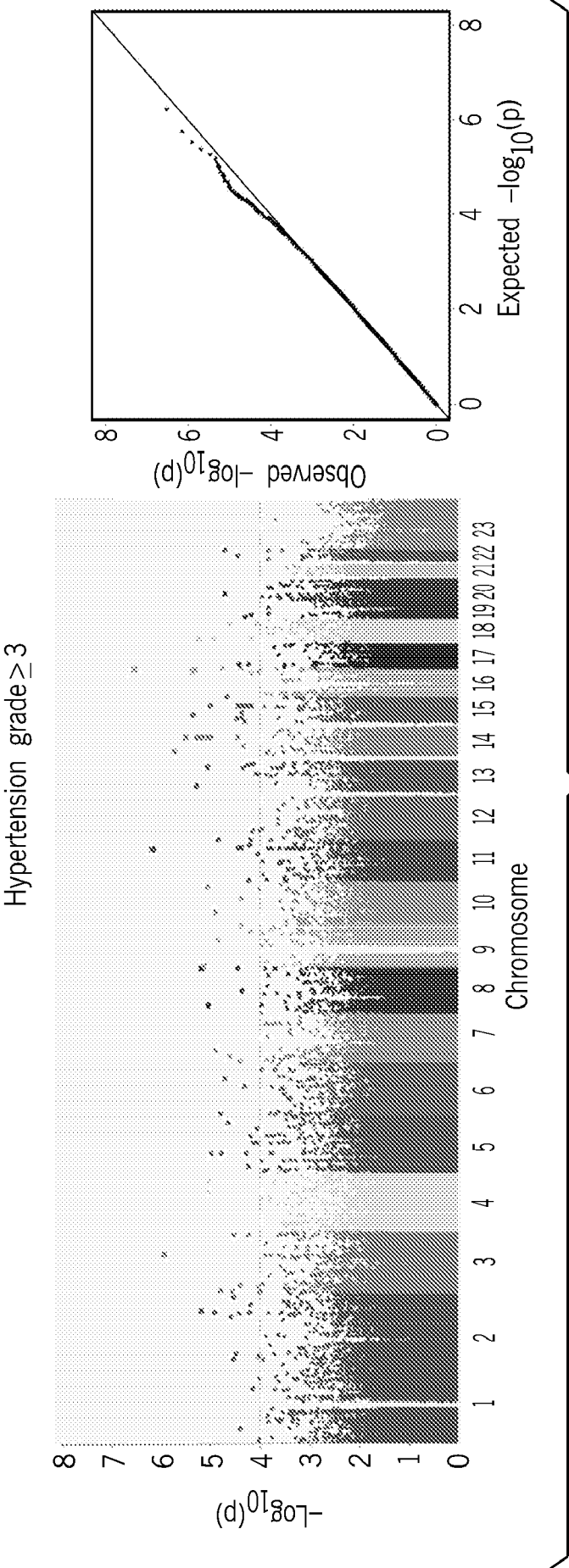


FIG. 5 (CONT.)

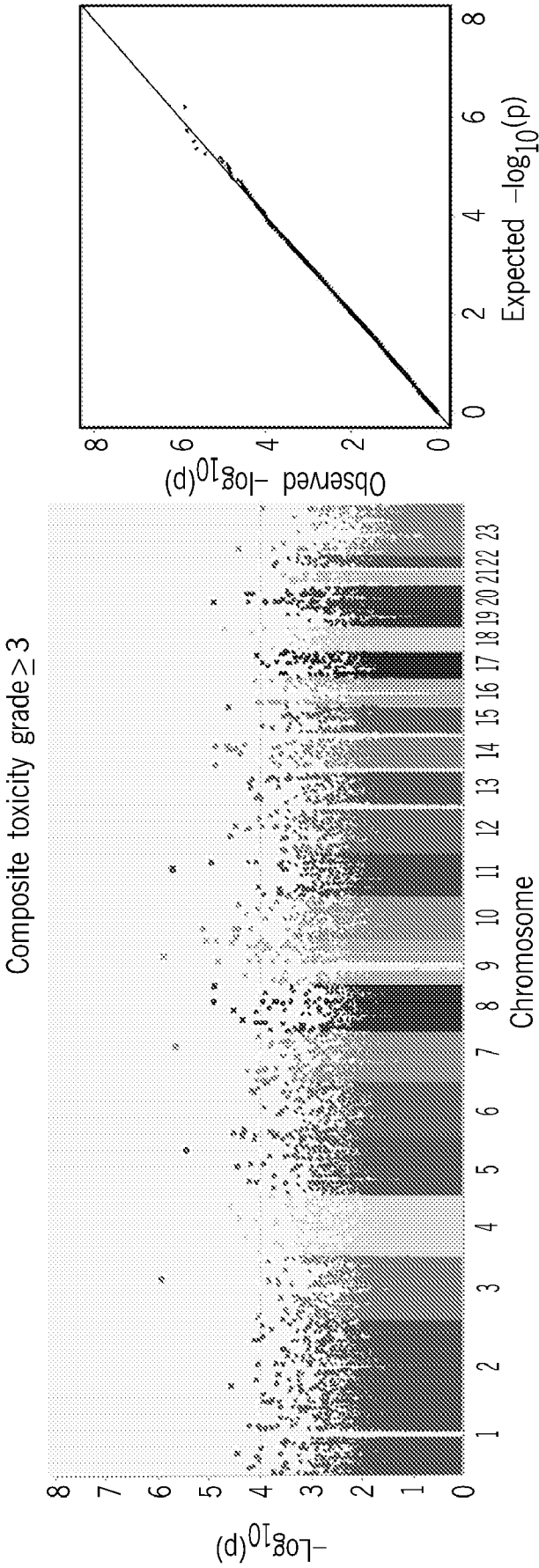


FIG. 5 (CONT.)

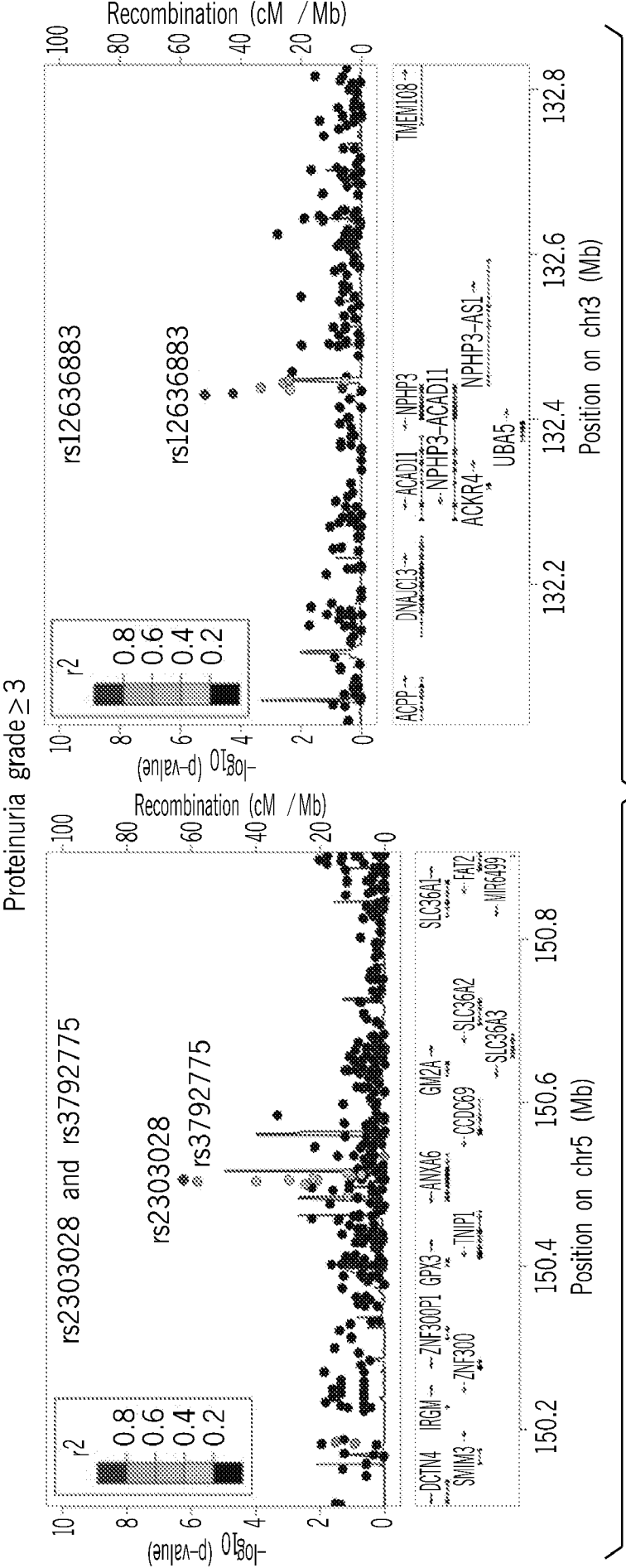


FIG. 6

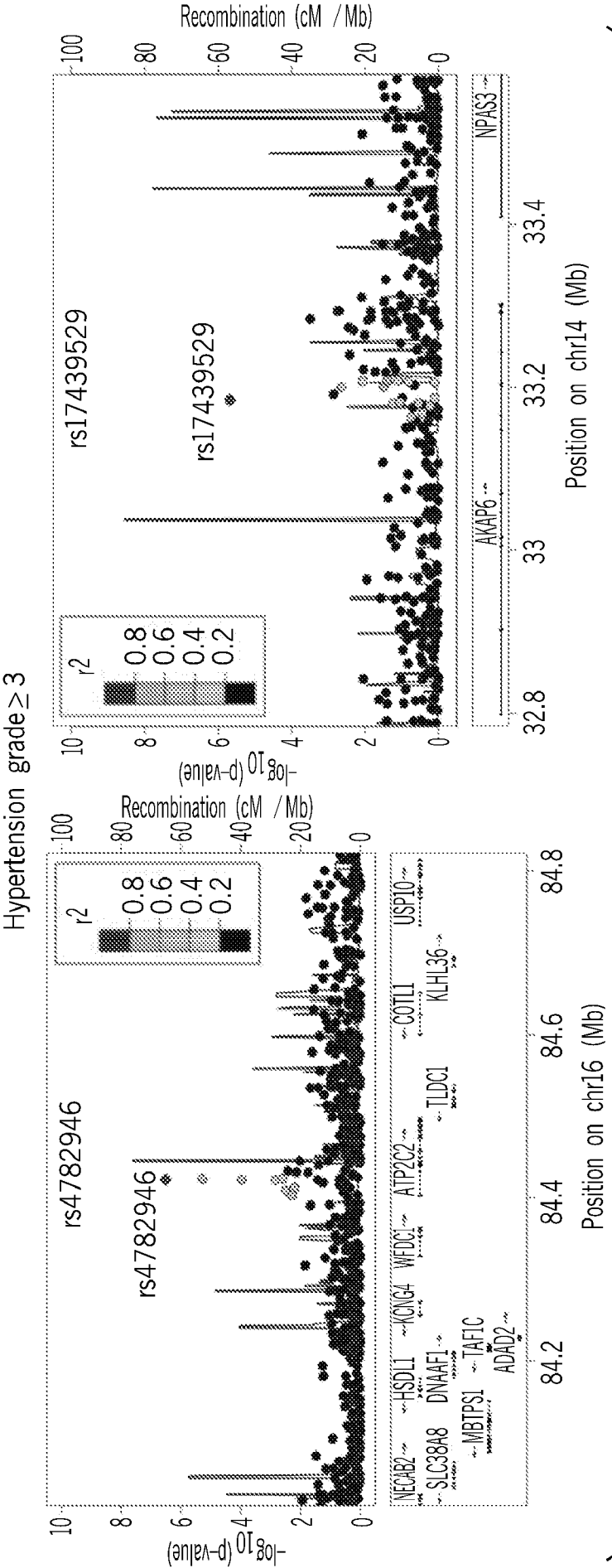


FIG. 6 (CONT.)

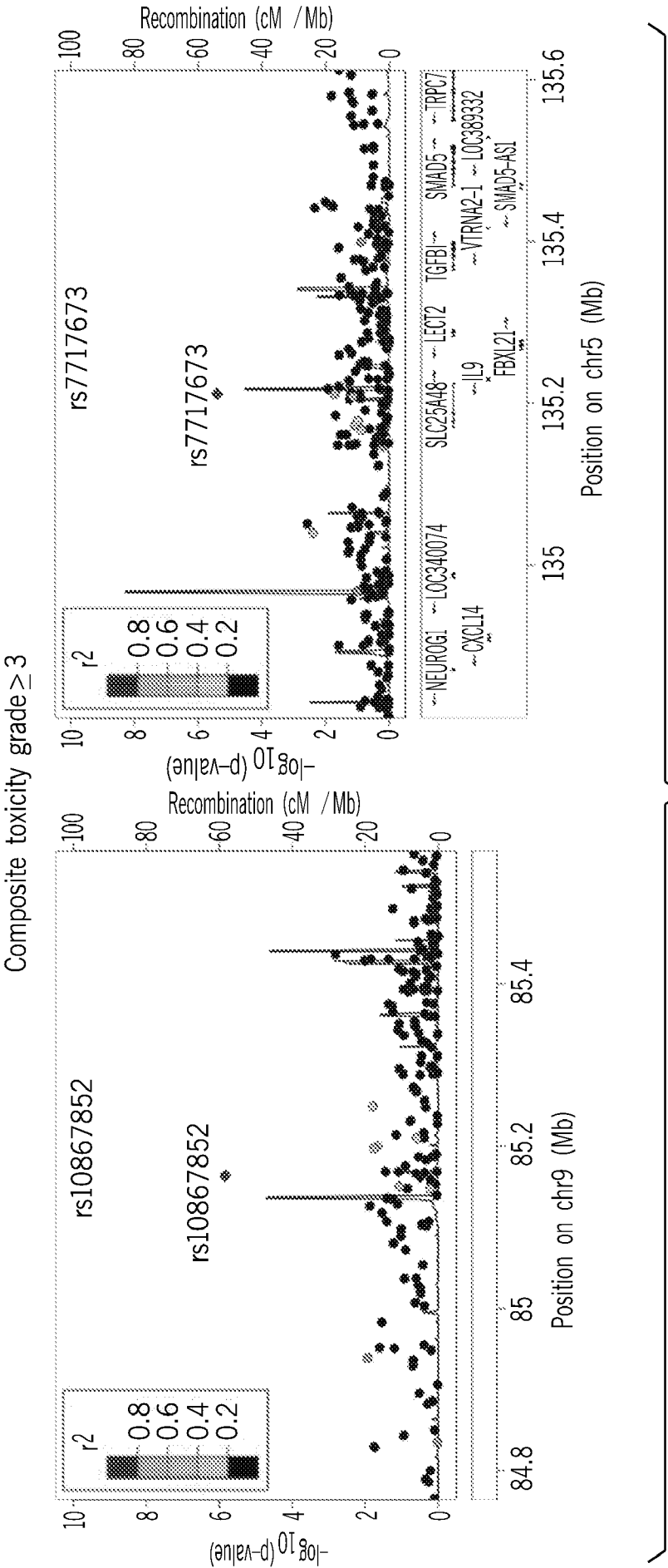


FIG. 6 (CONT.)

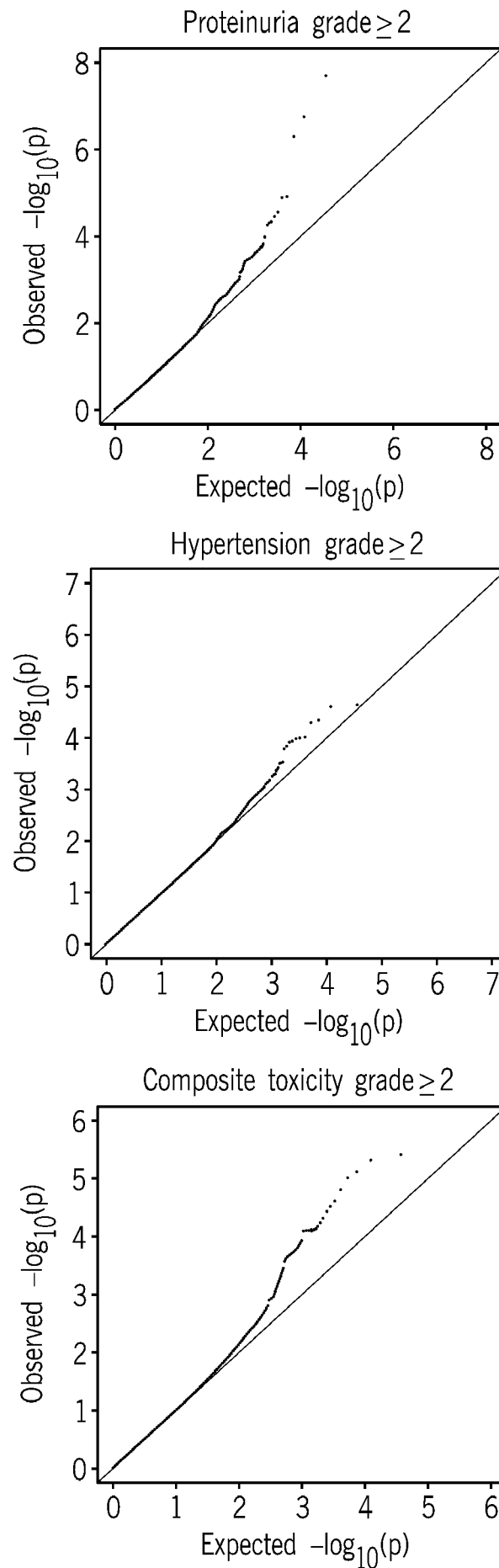


FIG. 7

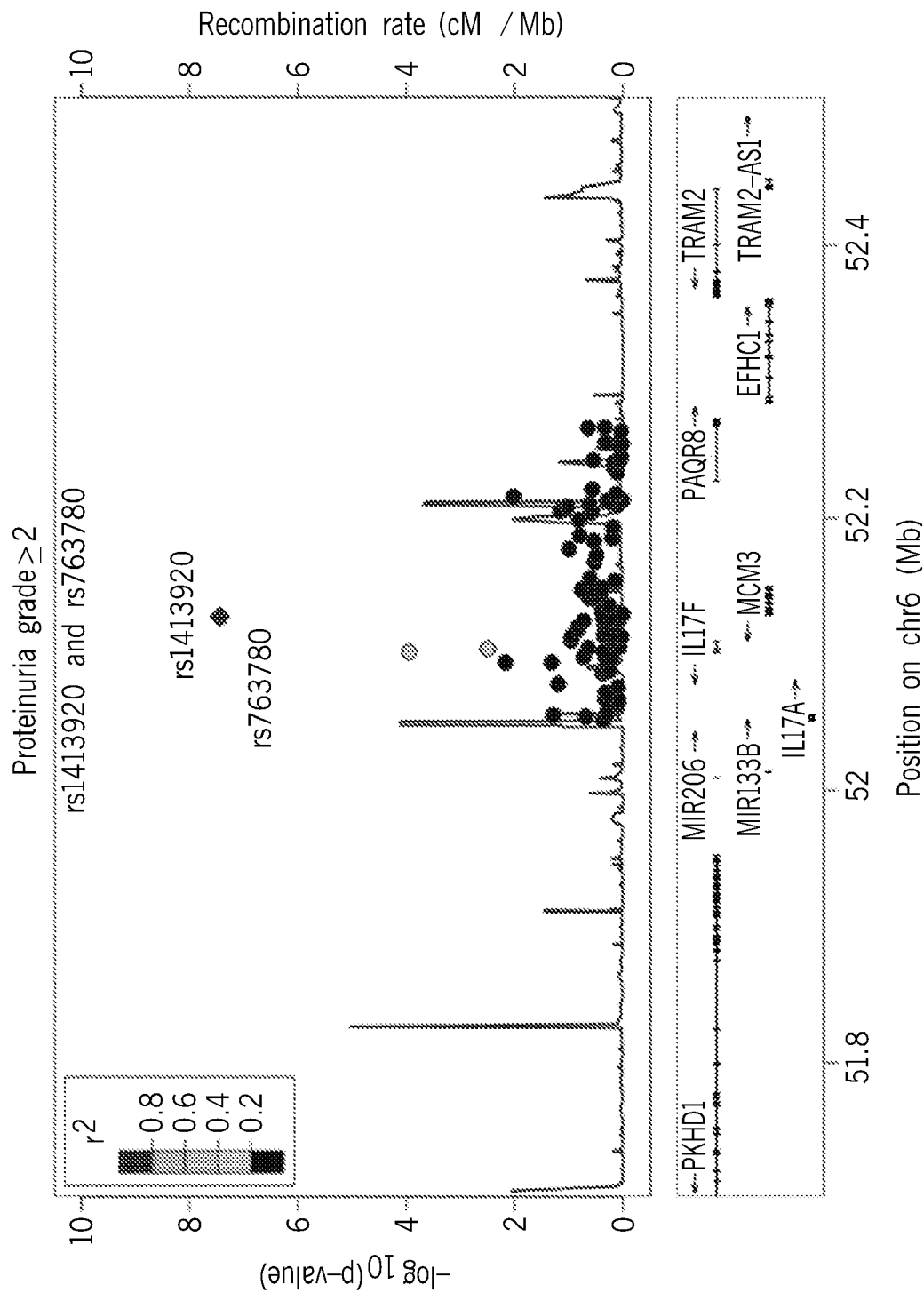


FIG. 8

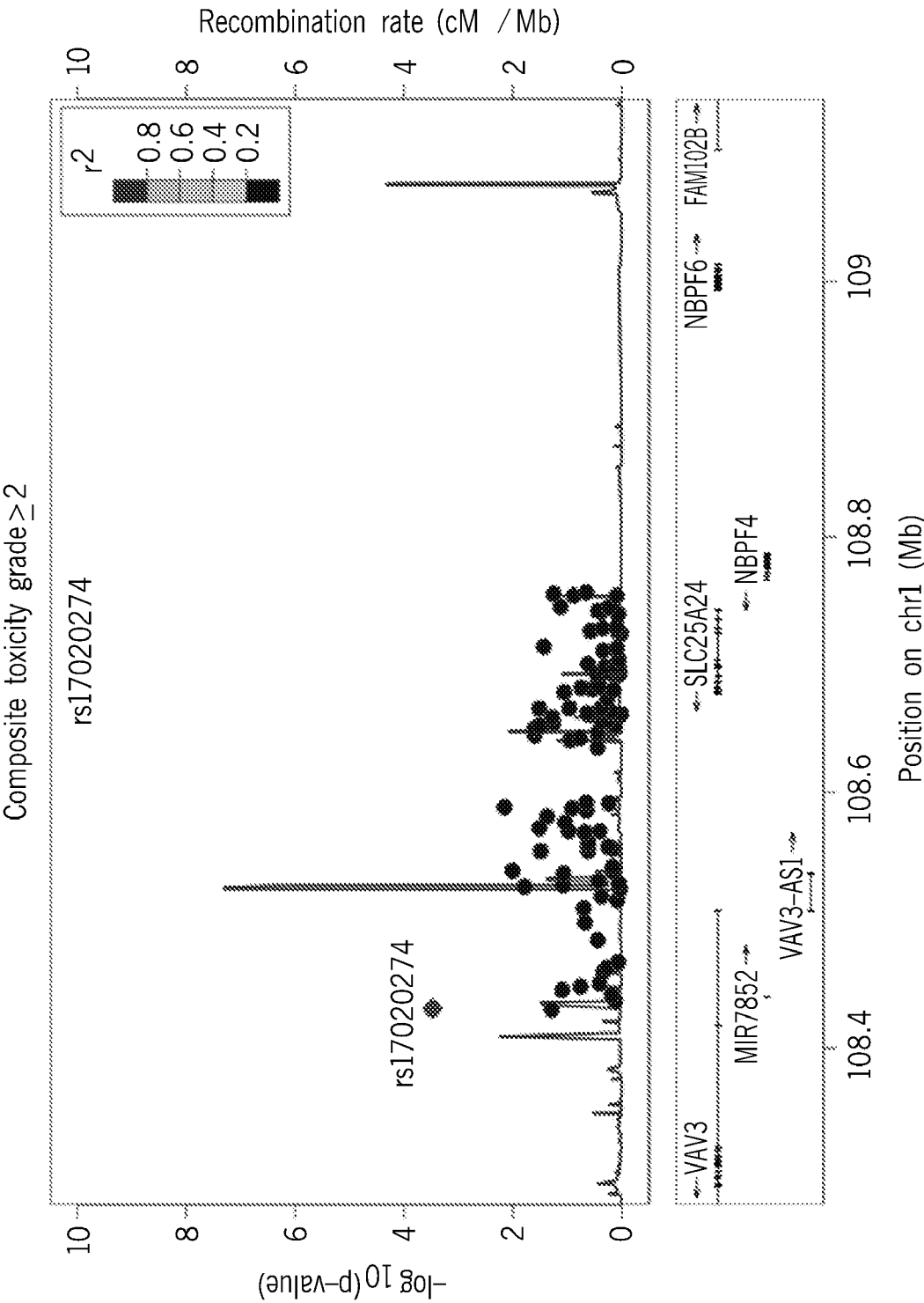


FIG. 8 (CONT.)

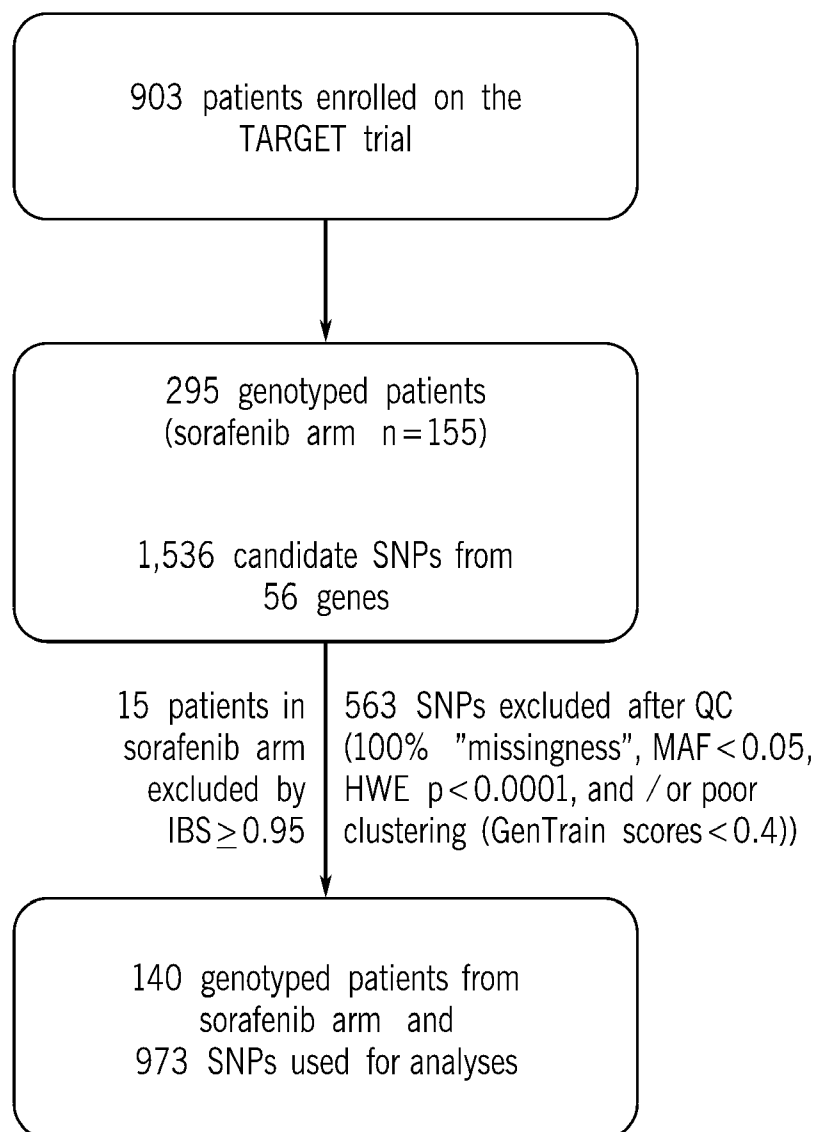


FIG. 9A

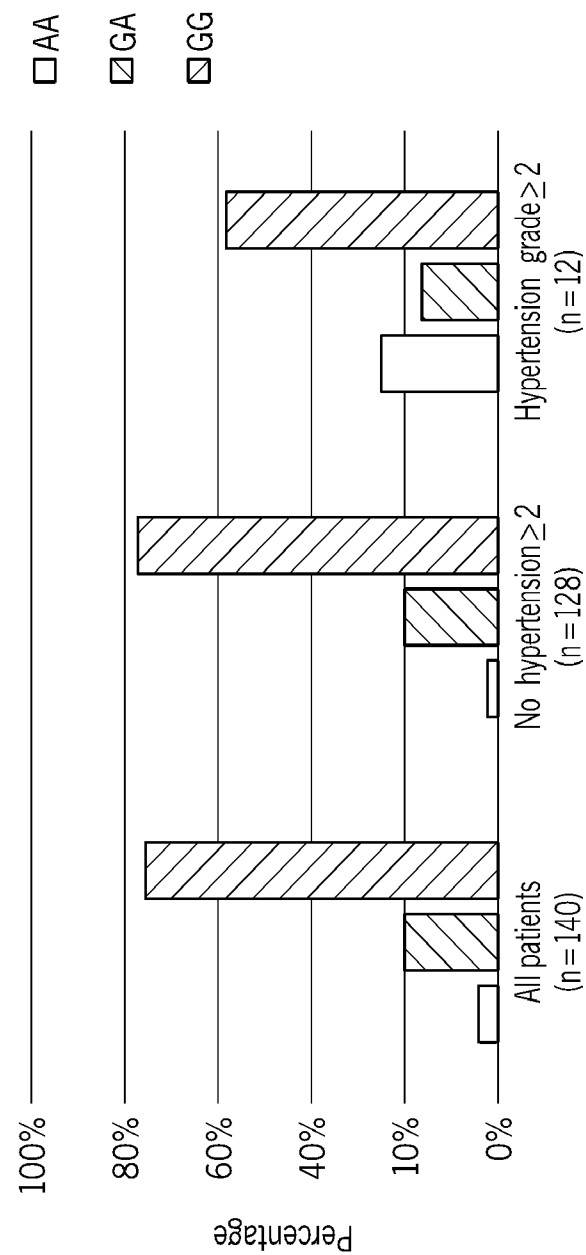


FIG. 9B

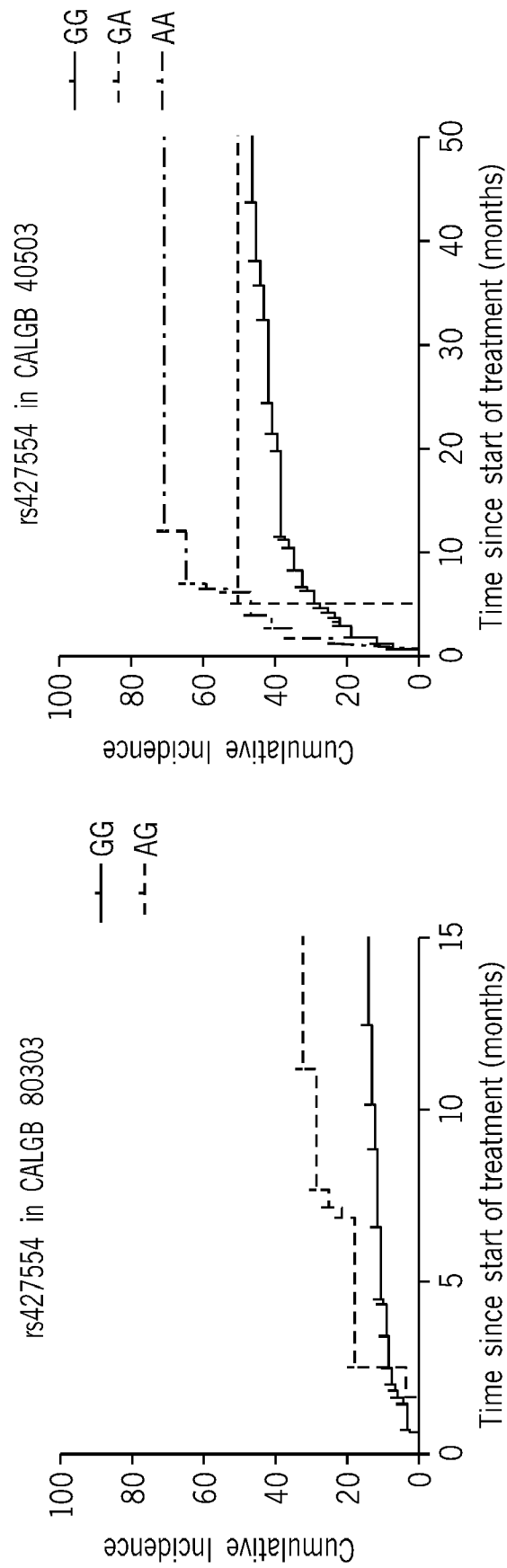


FIG. 10

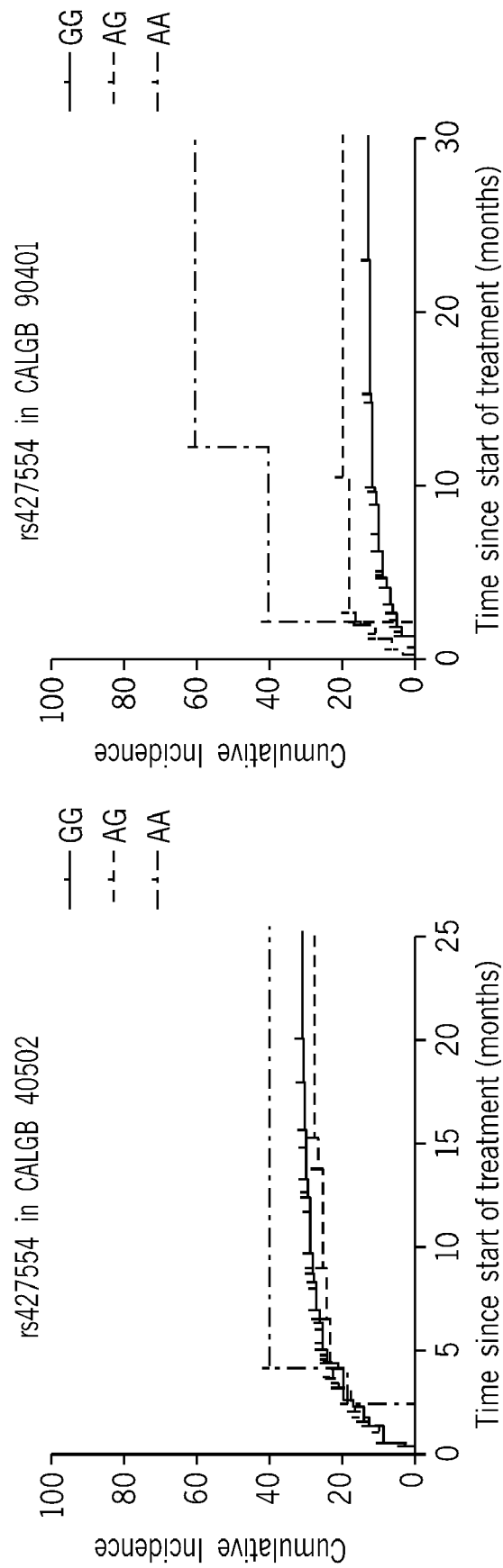


FIG. 10 (CONT.)

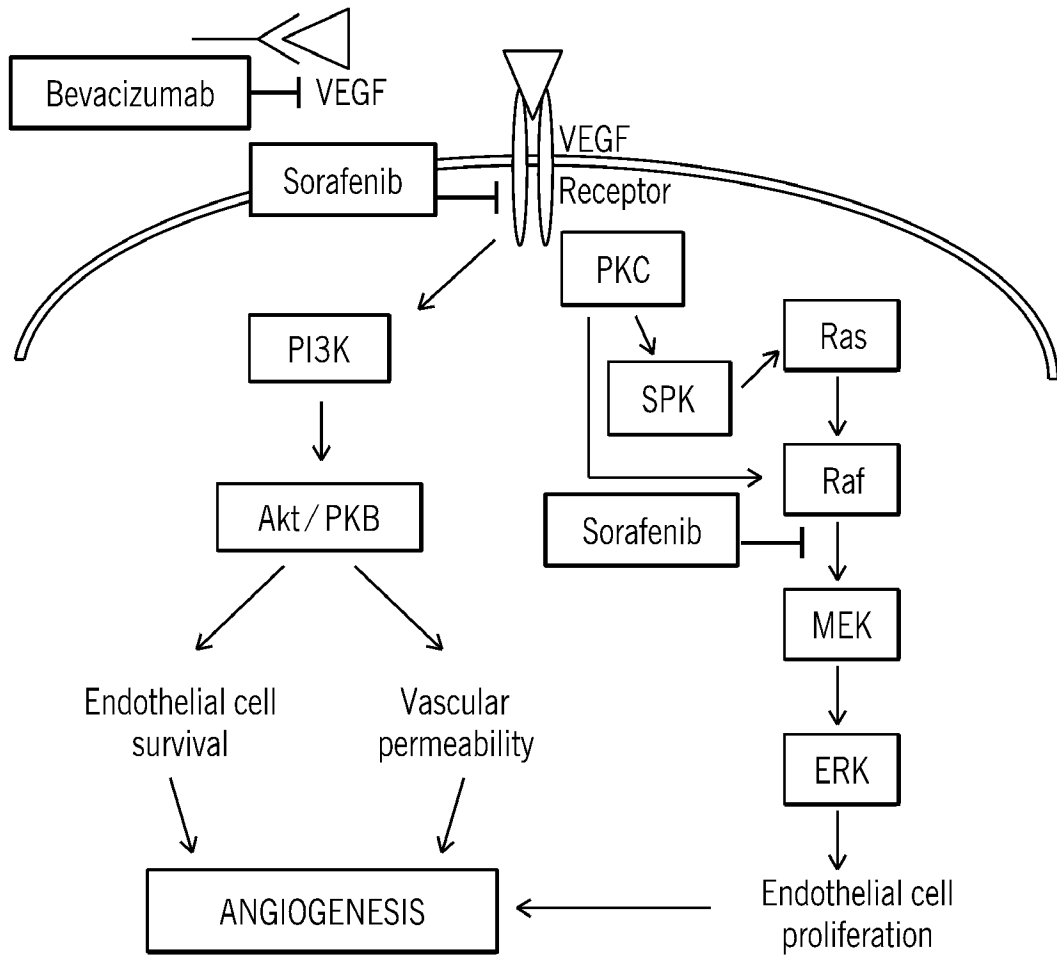
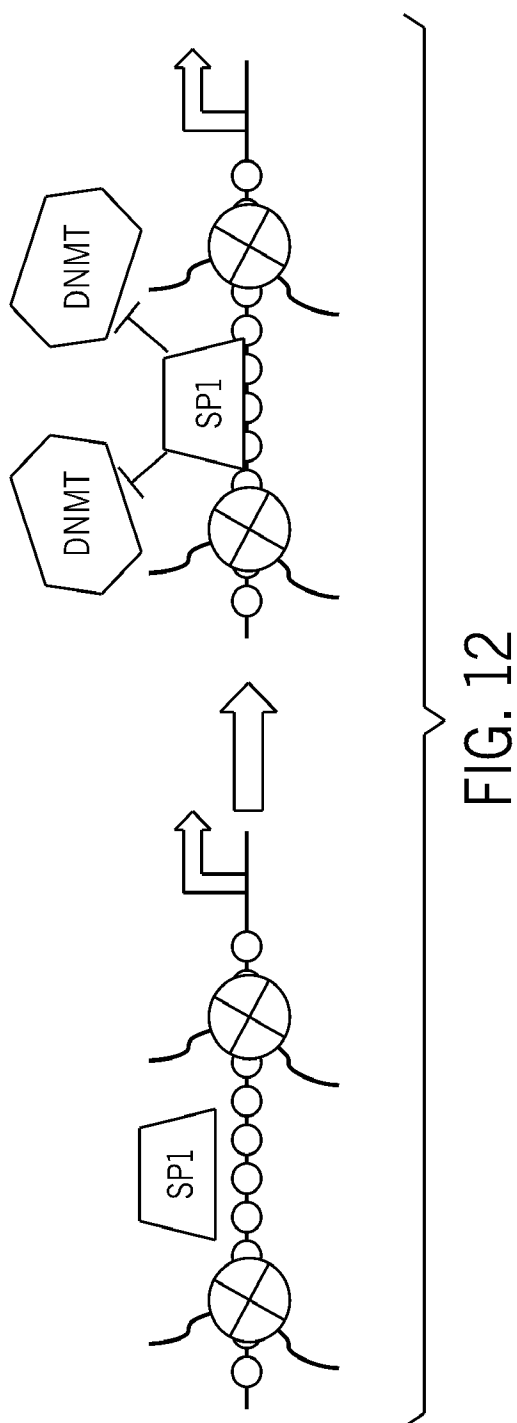


FIG. 11



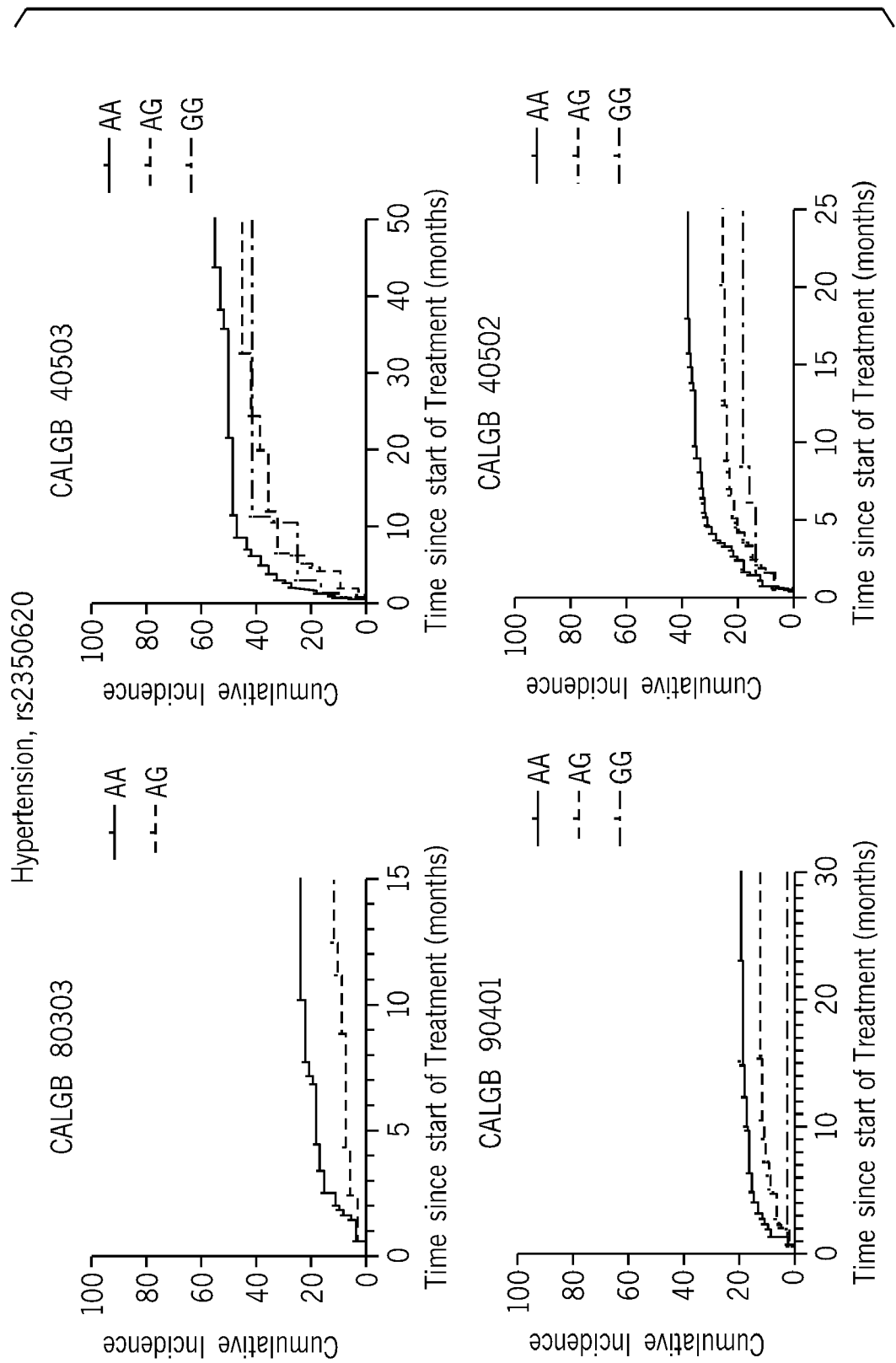


FIG. 13

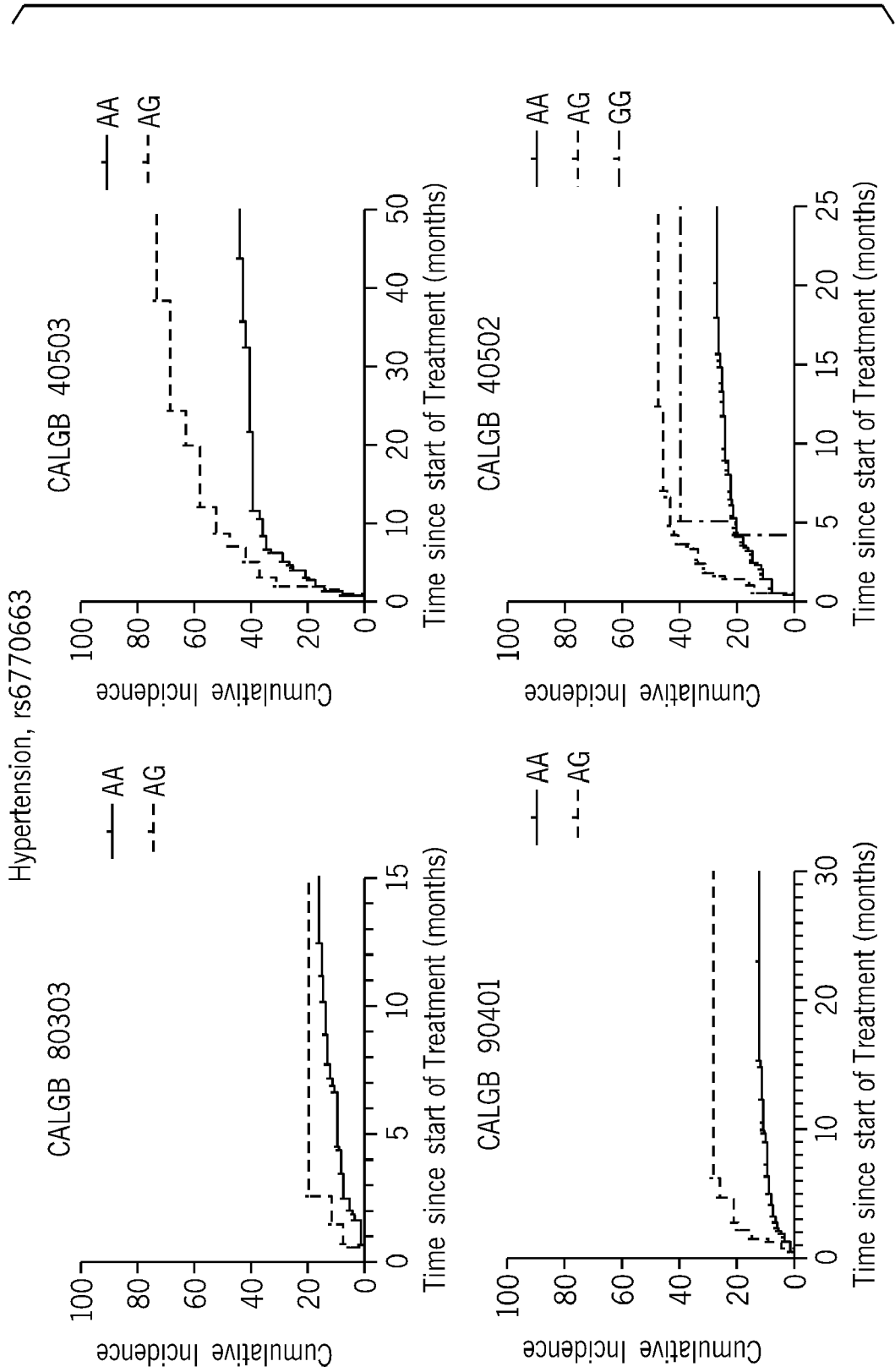


FIG. 13 (CONT.)

INTERNATIONAL SEARCH REPORT

International application No
PCT/US2020/042503

A. CLASSIFICATION OF SUBJECT MATTER
INV. C12Q1/6886
ADD.

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
C12Q

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)

EPO-Internal, EMBASE, BIOSIS, Sequence Search, WPI Data

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	SCHNEIDER B P ET AL: "Genetic variant predicts bevacizumab-induced hypertension in ECOG-5103 and ECOG-2100", BRITISH JOURNAL OF CANCER 20140909 NATURE PUBLISHING GROUP GBR, vol. 111, no. 6, 9 September 2014 (2014-09-09), pages 1241-1248, XP055740290, ISSN: 0007-0920 the whole document ----- -/-	1,2,8, 30-33



Further documents are listed in the continuation of Box C.



See patent family annex.

* Special categories of cited documents :

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier application or patent but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art

"&" document member of the same patent family

Date of the actual completion of the international search

16 October 2020

Date of mailing of the international search report

18/12/2020

Name and mailing address of the ISA/

European Patent Office, P.B. 5818 Patentlaan 2
NL - 2280 HV Rijswijk
Tel. (+31-70) 340-2040,
Fax: (+31-70) 340-3016

Authorized officer

Botz, Jürgen

INTERNATIONAL SEARCH REPORT

International application No

PCT/US2020/042503

C(Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	CRUCITTA STEFANIA ET AL: "Endothelial nitric oxide synthase c.-813C>T predicts for proteinuria in metastatic breast cancer patients treated with bevacizumab-based chemotherapy", CANCER CHEMOTHERAPY AND PHARMACOLOGY, SPRINGER VERLAG, BERLIN, DE, vol. 84, no. 6, 16 September 2019 (2019-09-16), pages 1219-1227, XP036920137, ISSN: 0344-5704, DOI: 10.1007/S00280-019-03933-Z [retrieved on 2019-09-16] the whole document	1-4,8, 30-33
X	BERGER MARTIN D ET AL: "Autophagy-related polymorphisms predict hypertension in patients with metastatic colorectal cancer treated with FOLFIRI and bevacizumab: Results from TRIBE and FIRE-3 trials", EUROPEAN JOURNAL OF CANCER, ELSEVIER, AMSTERDAM, NL, vol. 77, 26 March 2017 (2017-03-26), pages 13-20, XP029999967, ISSN: 0959-8049, DOI: 10.1016/J.EJCA.2017.02.020 the whole document	1-4,8, 30-33
X	WO 2013/030168 A1 (HOFFMANN LA ROCHE [CH]; VIB VZW [BE] ET AL.) 7 March 2013 (2013-03-07) the whole document	1-4,8, 13-15, 19,30-33
X	DI SALVATORE MARIANTONIETTA ET AL: "IL-8 and eNOS polymorphisms predict bevacizumab-based first line treatment outcomes in RAS mutant metastatic colorectal cancer patients", ONCOTARGET, vol. 8, no. 10, 7 March 2017 (2017-03-07), pages 16887-16898, XP055740422, the whole document	1-4,8, 30-33
A	GILLIAN M KEATING: "Bevacizumab: A Review of Its Use in Advanced Cancer", DRUGS, vol. 74, no. 16, 1 October 2014 (2014-10-01), pages 1891-1925, XP055449569, NZ ISSN: 0012-6667, DOI: 10.1007/s40265-014-0302-9 the whole document	1-64

-/--

INTERNATIONAL SEARCH REPORT

International application No
PCT/US2020/042503

C(Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
Y	MCCARTHY N ET AL: "GENE-CENTRIC STUDY IDENTIFIES TWO NOVEL GENES, CLCN2 AND KCNAB1, ASSOCIATED WITH BLOOD PRESSURE IN TWO INDEPENDENT IRISH POPULATIONS", JOURNAL OF HYPERTENSION, vol. 28, no. Suppl. A, June 2010 (2010-06), pages E341-E342, XP055740770, & 20TH ANNUAL MEETING OF THE EUROPEAN-SOCIETY-OF-HYPERTENSION; OSLO, NORWAY; JUNE 18 -21, 2010 ISSN: 0263-6352 the whole document	1-64
Y	----- YEN-FENG CHIU ET AL: "Identification of rare variants for hypertension with incorporation of linkage information", BMC PROCEEDINGS, BIOMED CENTRAL LTD, LONDON UK, vol. 8, no. Suppl 1, 17 June 2014 (2014-06-17), page S109, XP021188461, ISSN: 1753-6561, DOI: 10.1186/1753-6561-8-S1-S109 the whole document	1-64
A	----- WO 2011/084791 A2 (MAYO FOUNDATION; GAROVIC VESNA D) 14 July 2011 (2011-07-14) the whole document -----	1-64

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US2020/042503

Box No. II Observations where certain claims were found unsearchable (Continuation of item 2 of first sheet)

This international search report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. ☐ Claims Nos.:
because they relate to subject matter not required to be searched by this Authority, namely:
2. ☐ Claims Nos.:
because they relate to parts of the international application that do not comply with the prescribed requirements to such an extent that no meaningful international search can be carried out, specifically:
3. ☐ Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box No. III Observations where unity of invention is lacking (Continuation of Item 3 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

see additional sheet

1. ☐ As all required additional search fees were timely paid by the applicant, this international search report covers all searchable claims.
2. ☐ As all searchable claims could be searched without effort justifying an additional fees, this Authority did not invite payment of additional fees.
3. ☐ As only some of the required additional search fees were timely paid by the applicant, this international search report covers only those claims for which fees were paid, specifically claims Nos.:
4. ☒ No required additional search fees were timely paid by the applicant. Consequently, this international search report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

1-64(partially)

Remark on Protest

- ☐ The additional search fees were accompanied by the applicant's protest and, where applicable, the payment of a protest fee.
- ☐ The additional search fees were accompanied by the applicant's protest but the applicable protest fee was not paid within the time limit specified in the invitation.
- ☐ No protest accompanied the payment of additional search fees.

FURTHER INFORMATION CONTINUED FROM PCT/ISA/ 210

This International Searching Authority found multiple (groups of) inventions in this international application, as follows:

1. claims: 1-64(partially)

A method for detecting detecting a mutation in one or more nucleic acids in a sample obtained from a subject, wherein the subject is undergoing therapy or is a candidate for therapy with a VEGF-pathway inhibitor making use of rs339947, a method of predicting the risk of developing one or more VEGF-pathway inhibitor-induced toxicities in a subject, the use of rs339947 in a method according to underlying claim 3, a method of treating a subject according to the wording of underlying claims 13, 14, 34, 51 and making use of rs339947.

2-840. claims: 1-64(partially)

IDEM for inventions 2 - 840, whereby the SNP for invention 2 is the second SNP of Table 4 (= rs13293961) and the SNP of invention 840 is the last SNP mentioned in Table 13 (= rs7903829).

INTERNATIONAL SEARCH REPORT

Information on patent family members

International application No

PCT/US2020/042503

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
WO 2013030168 A1	07-03-2013	AR 087714 A1	09-04-2014
		AU 2012300986 A1	13-02-2014
		BR 112014004763 A2	21-03-2017
		CA 2845386 A1	07-03-2013
		CN 103946395 A	23-07-2014
		EP 2751280 A1	09-07-2014
		EP 3085793 A1	26-10-2016
		ES 2589455 T3	14-11-2016
		JP 2014526901 A	09-10-2014
		KR 20140064924 A	28-05-2014
		NZ 620343 A	28-10-2016
		RU 2014110270 A	10-10-2015
		SG 2014008585 A	28-04-2014
		US 2014294811 A1	02-10-2014
		WO 2013030168 A1	07-03-2013
		ZA 201400950 B	26-08-2015

WO 2011084791 A2	14-07-2011	AU 2010339723 A1	09-08-2012
		BR 112012017767 A2	24-09-2019
		CA 2785273 A1	14-07-2011
		EP 2517014 A2	31-10-2012
		ES 2530866 T3	06-03-2015
		JP 5753541 B2	22-07-2015
		JP 2013515268 A	02-05-2013
		US 2013034861 A1	07-02-2013
		US 2013296397 A1	07-11-2013
		US 2016060333 A1	03-03-2016
		US 2018002416 A1	04-01-2018
		WO 2011084791 A2	14-07-2011
