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Genetic predisposition to bevacizumab-induced hypertension

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HIGHLIGHTS

- Variation in *WNK1*, *KLKB1*, and *GRK4* may be associated with BIH.
- *WNK1*, *KLKB1*, and *GRK4* are biologically plausible mediators of BIH.
- A composite risk model identified 43% of patients who developed BIH.

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ABSTRACT

Objective. Bevacizumab, a monoclonal antibody to VEGF, has shown efficacy in ovarian, cervical and endometrial cancer in addition to several other solid tumors. Serious side effects include hypertension, proteinuria, bowel perforation, and thrombosis. We tested the hypothesis that genetic variation in hypertension-associated genes is associated with bevacizumab-induced hypertension (BIH).

Methods. Patients with solid tumors treated with bevacizumab in combination with other therapy were identified from six clinical trials. Haplotype-tagging (ht) SNPs for 10 candidate genes associated with hypertension were identified through the International Hapmap Project. Germline DNA was genotyped for 103 htSNPs using mass spectrometry. Bevacizumab toxicities were identified from clinical trial reports. Haplotypes were reconstructed from diploid genotyping data and frequencies were compared using standard two-sided statistical tests.

Results. The study included 114 patients with breast, lung, ovarian, or other cancers, of whom 38 developed BIH. *WNK1*, *KLKB1*, and *GRK4* were found to contain single loci associated with BIH. Haplotype analysis of *WNK1*, *KLKB1*, and *GRK4* identified risk haplotypes in each gene associated with grade 3/4 BIH. A composite risk model was created based on these haplotypes. Patients with the highest risk score were the most likely to develop grade 3/4 BIH (OR = 6.45; $P = 0.005$; 95%CI, 1.86–22.39).

Conclusions. We concluded that genetic variation in *WNK1*, *KLKB1*, and *GRK4* may be associated with BIH. These genes are biologically plausible mediators due to their role in blood pressure control, regulating sodium homeostasis and vascular tone. This preliminary risk model performed better than population-based risk models and when further validated may help risk-stratify patients for BIH prior to initiating therapy.

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1. Introduction

Bevacizumab is a recombinant monoclonal antibody to vascular endothelial growth factor (VEGF). VEGF binds to endothelial cell receptors and promotes tumor angiogenesis by encouraging endothelial cell proliferation, migration and survival, and increasing vascular permeability. The efficacy of bevacizumab as an anti-cancer agent relies on its

inhibition of the angiogenesis-promoting biological functions of VEGF [1]. Bevacizumab is currently FDA approved for the treatment of cervical cancer [2], ovarian cancer [3–5], colorectal cancer [6], glioblastoma [7], non-small-cell lung cancer [8,9], renal cell cancer [10] and has shown activity in many other tumors including endometrial [11], breast [12], soft tissue sarcomas [13] and malignant mesothelioma [14] as a single agent or in combination with cytotoxic agents.

Studies of bevacizumab have demonstrated that inhibition of VEGF induces or exacerbates hypertension in some patients and can cause other serious side effects including thrombosis, wound-healing complications, hemorrhage, gastrointestinal perforation, and proteinuria.

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Table 1
Candidate hypertension-associated genes.

Renin-angiotensin-aldosterone system
Angiotensinogen (AGT)
Angiotensin II Type 1 Receptor (AGTR1)
Aldosterone Synthase (CYP11B2)
Angiotensin-1-converting Enzyme (ACE)
Bradykinin-related
Bradykinin Receptor 1 (BDKRB1)
Kallikrein (KLKB1)
Sodium Regulation
WNK1 (with no lysine K)
G Protein-coupled Receptor Kinase 4 (GRK4)
Epithelial Sodium Channel
(ENaC- α /SCNN1a)
G Protein B3 Subunit (GNB3)
Vascular Endothelial Growth Factor (VEGF)

According to a meta-analysis of 12,656 patients with a variety of tumors receiving bevacizumab, the incidence of hypertension was 23.6%. The incidence of severe hypertension, defined as National Cancer Institute Common Toxicity Criteria grade 3 or 4, was 7.9%, and the relative risk for developing severe hypertension was 5.3. This increased risk was observed with both low- and high-dose bevacizumab regimens [15]. Another meta-analysis reviewing 9062 patients receiving bevacizumab found the relative risk of all-grade hypertension to be 5.3 [16]. Other studies have reported rates of severe hypertension in patients receiving bevacizumab ranging from 15 to 25% [17,18]. The mechanism of bevacizumab-induced hypertension remains unclear.

Scientific advances have altered the study of the genetic epidemiology of complex diseases. The International HapMap Project database provides a catalog of the common human genetic variants across several populations [19,20]. These data have resulted in a shift away from linkage analysis towards association mapping of genes that affect complex phenotypes. HapMap has catalogued the block structure, or haplotype pattern, of the human genome. By exploiting the underlying patterns of linkage disequilibrium (LD), it is possible to use haplotype-based association studies to identify disease susceptibility alleles [21]. Specific haplotype blocks may contain genetic variants involved in susceptibility to disease [22]. Haplotype analysis has resulted in the publication of a series of studies that examine potential genetic contributions to common diseases, including prostate cancer, breast cancer, diabetes, and coronary artery disease [23]. Furthermore, haplotype analysis has been used to predict medication side effects [24].

Association studies are especially useful for complex disorders like hypertension, in which multiple genetic factors interact with the environment to determine phenotype. Familial and epidemiological studies suggest that 30–50% of blood pressure variation is genetic in origin [25]. Genes involved in complex diseases, like hypertension, have been discovered through linkage mapping. This method successfully identified genes for several rare monogenic forms of blood pressure deregulation, but no single gene has been found to have a major effect on blood pressure variation in the general population. However, these Mendelian hypertensive disorders highlight potential pathways and mechanisms of hypertension and provide candidate genes for genetic association research [26]. Genetic variation in several blood pressure deregulation-associated genes has been associated with hypertension [27–30].

Almost one third of patients treated with bevacizumab develop hypertension, which might imply that common variation present in the population contributes to the susceptibility for this toxicity. Previous studies have examined genetic variation in hypertension-associated candidate genes and identified polymorphisms and haplotypes associated with essential hypertension. The purpose of the study was to test the hypothesis that genetic variation in hypertension-associated genes is associated with the risk for developing bevacizumab-induced hypertension.

2. Methods

2.1. Study population

Cases and controls were collected from one of six ongoing or completed IRB-approved protocols at Memorial Sloan-Kettering Cancer Center (Supplementary Table S1). This study was also specifically approved by the local IRB and written consents were obtained from all patients. In these protocols, bevacizumab is used in combination with chemotherapy agents, molecularly targeted agents, or hormonal agents for patients with breast cancer, non-small-cell lung cancer, serous ovarian cancer, and other advanced solid tumors. All patients were white as a result of the demographics of the patient population treated at this institution during the study time period and to limit genetic heterogeneity. Hypertension was graded according to the National Cancer Institute Common Toxicity Criteria version 3.0 (ctepcancer.gov) and recorded as part of the protocol. Patients with existing uncontrolled hypertension at time of enrollment, defined as systolic blood pressure >150 or diastolic blood pressure >90, were excluded from the trial. Hypertension that developed while on treatment protocols was managed by protocol guidelines outlined in Supplementary Table 2. All patients included in this study had undergone surgical resection or excisional biopsy of their disease. Benign tissue removed at the time of surgery was used for DNA extraction. Clinical information was extracted from institutional, research, and laboratory databases.

2.2. Candidate genes and SNP selection

Eleven candidate genes were identified from a review of the literature on hypertension and genetic variation that contributes to blood pressure regulation (Table 1). These genes fit into one of four categories based on the mechanism of blood pressure regulation: genes involved in the renin-angiotensin-aldosterone system, genes related to bradykinin, genes involved in sodium regulation, and VEGF, the gene implicated in the activity of bevacizumab. We identified single nucleotide polymorphisms (SNPs) within these genes from www.hapmap.org. Polymorphisms were selected for each gene provided that the minor allele frequency was >0.05 in the CEPH population (Utah Residents with Northern and Western European Ancestry, CEU). Haplotype-tagging SNPs (htSNPs) were selected using Tagger (www.broadinstitute.org/mpg/tagger) to capture the unmeasured SNPs with a minor allele frequency ≥ 0.05 and $r^2 \geq 0.8$. One hundred and ten SNPs in 11 genes were initially selected for analysis (Supplementary Table S2). SNPs below a genotyping call rate of 95% were removed ($n = 7$), leaving 103 SNPs in 11 genes for statistical analysis.

2.3. Genotyping and quality control

Genomic DNA was prepared from peripheral lymphocytes using QIAGEN DNeasy Blood and Tissue kit (QIAGEN Inc., Valencia, CA).

Table 2
Patient characteristics.

Gender	n (%)
Male	19 (17)
Female	95 (83)
Disease site	n (%)
Breast	55 (48)
Non-small cell lung cancer	25 (22)
Serous ovarian cancer	19 (17)
Advanced solid tumor	15 (13)
Hypertension grade	n (%)
Grades I–IV	38 (33)
Grade I	6 (5)
Grade II	18 (16)
Grade III	13 (11)
Grade IV	1 (1)

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