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Phenome-Wide Association Study of *UMOD* Gene Variants and Differential Associations With Clinical Outcomes Across Populations in the Million Veteran Program a Multiethnic Biobank

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Introduction: Common variants in the *UMOD* gene are considered an evolutionary adaptation against urinary tract infections (UTIs) and have been implicated in kidney stone formation, chronic kidney disease (CKD), and hypertension. However, differences in *UMOD* variant-phenotype associations across population groups are unclear.

Methods: We tested associations between *UMOD/PDILT* variants and up to 1528 clinical diagnosis codes mapped to phenotype groups in the Million Veteran Program (MVP), using published phenome-wide association study (PheWAS) methodology. Associations were tested using logistic regression adjusted for age, sex, and 10 principal components of ancestry. Bonferroni correction for multiple comparisons was applied.

Results: Among 648,593 veterans, mean (SD) age was 62 (14) years; 9% were female, 19% Black, and 8% Hispanic. In White patients, the rs4293393 *UMOD* risk variant associated with increased uromodulin was associated with increased odds of CKD (odds ratio [OR]: 1.22, 95% CI: 1.20–1.24, $P = 5.90 \times 10^{-111}$), end-stage kidney disease (OR: 1.17, 95% CI: 1.11–1.24, $P = 2.40 \times 10^{-09}$), and hypertension (OR: 1.03, 95% CI: 1.05–1.05, $P = 2.11 \times 10^{-06}$) and significantly lower odds of UTIs (OR: 0.94, 95% CI: 0.92–0.96, $P = 1.21 \times 10^{-10}$) and kidney calculus (OR: 0.85, 95% CI: 0.83–0.86, $P = 4.27 \times 10^{-69}$). Similar findings were observed across *UMOD/PDILT* variants. The rs77924615 *PDILT* variant had stronger associations with acute cystitis in White female (OR: 0.73, 95% CI: 0.59–0.91, $P = 4.98 \times 10^{-03}$) versus male (OR: 0.99, 95% CI: 0.89–1.11, $P = 8.80 \times 10^{-01}$) (P interaction = 0.01) patients. In Black patients, the rs77924615 *PDILT* variant was significantly associated with pyelonephritis (OR: 0.65, 95% CI: 0.54–0.79, $P = 1.05 \times 10^{-05}$), whereas associations with *UMOD* promoter variants were attenuated.

Conclusion: Robust associations were observed between *UMOD/PDILT* variants linked with increased uromodulin expression and lower odds of UTIs and calculus and increased odds of CKD and hypertension. However, these associations varied significantly across ancestry groups and sex.

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Uromodulin (Umod) is an 85-kilodalton glycoprotein that is exclusively synthesized in the kidney by epithelial cells of the thick ascending limb of the loop of Henle and the distal convoluted tubule.[1–3] It is the most abundant protein in healthy human urine.[4,5] Umod is encoded by the *UMOD* gene on chromosome 16p12.3.[6–8]

Prior studies have suggested several physiological roles including regulation of ion (sodium ion and potassium ion) transport by interactions with the NKCC2 cotransporter and the ROMK channel[9,10]; defense against UTIs by binding uropathogenic *Escherichia coli*[11–13]; preventing formation of calculi by impairing aggregation of calcium oxalate crystals[14]; and playing a role in innate immunity by binding immunoglobulins and cytokines or activating monocytes and dendritic cells by Toll-like receptor 4.[15,16]

Recent genetic studies revealing common *UMOD* variants as important contributors to the architecture of renal traits (across multiple populations)[17–21] and blood pressure,[22] have reignited interest in Umod physiology. Because *UMOD* risk variants directly increase Umod expression,[23,24] assessing their effect on clinically relevant phenotypes is paramount. More importantly, there may be relevant differences in the association between *UMOD* risk variants and clinical phenotypes across different ancestry groups given documented heterogeneity in the genetic basis of complex traits across population groups.[25] However, this has been underexplored. We performed a PheWAS of common *UMOD* variants in non-Hispanic White, Black, Asian, and Hispanic patients in the MVP to investigate the pleiotropic effects of increased Umod expression on clinically relevant phenotypes and to evaluate differences in *UMOD*-phenome associations between population groups.

METHODS

The data that support the findings of this study are available from the corresponding author on reasonable request.

Study Design

This study was designed as a PheWAS, which is a bioinformatics approach that enables the scanning of a broad range of clinical phenotypes (the clinical phenome) available in the electronic health record (EHR) of patients for associations with a genetic variant so as to evaluate the pleiotropic effects in several clinical phenotypes that share genetic architecture.[26–29]

Study Population for Primary Analysis

The main study population for this study was participants enrolled in the MVP, which is a large multiethnic longitudinal cohort and mega biobank designed to investigate the genetic underpinnings of common medical conditions among US veterans.[30] The MVP data combine EHR data with genomic data to facilitate bioinformatic investigations. Full details of the MVP design and methods have been published elsewhere.[30] Briefly, participants were recruited from 63 Veterans Affairs clinics beginning in 2011. At enrolment, participants provided blood samples for genotyping and biomarker studies and completed baseline questionnaires for demographic and lifestyle data. Participants also agreed for their medical records to be accessed. The study was approved by the Veterans Affairs Central Institutional Review Board, and patients signed informed consent. For the current study, 648,593 MVP participants (Table 1 and Figure 1) who had available genotyping and phenotypic data at the time of this study were included in this PheWAS.

MVP Genotyping

Genotyping was performed using a customized Affymetrix Axiom Biobank Array using DNA extracted from whole blood[31] with content added to provide coverage of African and Hispanic haplotypes. Details of the MVP genotyping methods have been described elsewhere.[30,32,33] Briefly, standard QC and genotype calling algorithms were applied to the data using the Affymetrix Power Tools Suite. Duplicate samples and samples with an excess of missing genotype calls or a discordance of genetically inferred sex versus self-report were excluded. Related individuals as measured by the KING software[34] were also excluded. Before imputation, poorly called variants or single nucleotide polymorphisms (SNPs) deviating from their expected allele frequency based on the 1000 genomes reference panel (1000G)[35] were excluded.[33] After prephasing using EAGLE version 2,[36] genotypes from the 1000G[37] reference panel were imputed into MVP participants by Minimac3 software.[38] Principal component analysis was performed using the FlashPCA,[39] to generate the top 30 principal components explaining the greatest variability in ancestry. After the imputation, variant-level quality control was performed using the EasyQC R package,[40] and the following exclusion benchmarks were applied[41]: ancestry-specific Hardy–Weinberg equilibrium[42] $P < 1 \times 10^{-20}$, posterior call probability <0.9, imputation quality (r^2) or INFO score <0.3, minor allele frequencies (MAFs) <0.03%, call rate <97.5% for common variants (MAF >1%), and call rate <99% for rare variants (MAF <1%). Variants were also excluded if they deviated

Table 1. Demographic characteristics and clinical phenotypes captured by phecodes in Million Veteran Program participants

Characteristics	Non-Hispanic Whites n^a = 464,961			Non-Hispanic Blacks n^a = 123,120			Hispanics n^a = 52,183		
Demographics									
Age, mean (SD)	64 (14)			58 (12)			55 (16)		
Female, *n* (%)	34,438 (7.4)			16,993 (13.8)			5142 (9.9)		
Years of follow-up in the EHR, median (25th, 75th)	13.2 (8.0, 17.7)			15.0 (9.3, 18.9)			12.3 (6.5, 17.1)		
General comorbidities	**%**	**Cases**	**All[b]**	**%**	**Cases**	**All[b]**	**%**	**Cases**	**All[b]**
Hypertension	74.7	303,313	406,067	80.1	87,895	109,752	62.8	28,089	44,710
Type 2 diabetes	35.1	144,376	411,196	43.5	47,407	109,088	39.2	17,827	45,496
Gout	9.3	38,796	417,943	11.9	13,193	111,141	6.0	2789	46,404
Proteinuria	2.2	9030	420,081	3.9	4357	110,957	3.4	1544	46,086
Kidney disease									
Hypertensive heart and/or renal disease	13.3	53,251	399,633	18.6	19,685	106,142	10.3	4625	44,866
Hypertensive CKD	7.4	30,565	411,933	11.6	12,633	109,157	6.2	2842	45,956
Type 2 diabetes with renal manifestations	5.2	21,706	417,549	7.6	8393	110,764	6.1	2817	45,597
CKD	13.8	56,757	411,325	17.8	19,540	109,540	10.4	4795	45,904
CKD, stage I or II	2.0	8236	419,746	4.1	4583	110,618	1.8	829	46,453
CKD, stage III	8.9	37,099	416,227	10.7	11,929	111,092	6.7	3083	46,295
CKD, stage IV	2.1	8918	425,070	3.5	3953	113,406	2.4	1133	47,003
End-stage kidney disease	1.2	5334	426,352	3.4	3873	113,748	2.1	1011	47,056
Complications of CKD									
Anemia in CKD	1.7	7330	423,505	3.9	4347	112,692	2.3	1056	46,817
Anemia of chronic disease	3.3	13,675	416,793	6.0	6641	110,416	3.4	1593	46,254
Other anemias	19.6	76,540	390,181	28.9	29,742	102,918	16.4	7150	43,696
Hyperpotassemia	3.8	15,510	411,143	4.1	4517	110,276	3.4	1567	45,792
Secondary hyperparathyroidism (renal)	1.1	4716	426,008	2.5	2860	113,514	1.5	686	47,045
UTI complications									
UTI	10.7	42,133	394,057	13.6	13,886	102,047	10.4	4488	43,273
Pyelonephritis	0.7	2816	424,496	0.7	797	113,362	0.8	364	46,780
E. coli infection	0.5	2217	422,520	0.6	711	112,696	0.5	231	46,584
Urolithiasis-related phenotypes									
Hematuria	9.0	36,418	404,436	10.3	11,005	106,978	8.4	3746	44,558
Gross hematuria	3.1	12,904	418,551	3.5	3922	111,742	2.5	1175	46,339
Urinary calculus	8.8	36,238	412,276	4.8	5323	111,169	7.2	3289	45,729
Calculus of kidney	7.3	30,249	413,504	4.0	4435	111,594	5.9	2713	45,798
Calculus of ureter	2.1	8817	422,749	1.1	1201	113,737	1.7	775	46,716
Calculus of lower urinary tract	0.6	2784	425,792	0.4	394	114,151	0.4	209	47,081
Hydronephrosis	1.5	6559	422,000	1.2	1354	113,350	1.1	530	46,632
Stricture/obstruction of ureter	0.6	2478	427,241	0.5	534	113,677	0.5	223	46,860

CKD, chronic kidney disease; *E. coli*, *Escherichia coli*; EHR, electronic health record; PheWAS, phenome-wide association study; UTI, urinary tract infection.
[a]Represents the group-specific sample size with genotype and phenotype data.
[b]Represents the total number of cases + controls for each phenotype after the PheWAS algorithm but excluded patients not meeting the phecode-specific case or control definition.

by >10% from their expected allele frequency based on the 1000 genomes reference data.[43]

Race/Ethnicity/Ancestry in MVP

Racial/ethnic groups in the MVP were assigned using a harmonized ancestry and race/ethnicity variable based on an algorithm that integrates genetically inferred ancestry based on the top 30 principal components with self-identified race/ethnicity. Details have been described elsewhere.[25] On the basis of the harmonized ancestry and race/ethnicity variable, MVP participants with genotype data are assigned to 1 of the following 4 nonoverlapping groups: non-Hispanic White, non-Hispanic Black, non-Hispanic Asian, and Hispanic patients.

UMOD/*PDILT* Genetic Variants

The common *UMOD* variants referenced in this study are synonymous SNPs identified in genome-wide association studies (GWASs) of renal traits, blood pressure, and urinary uromodulin that in individuals of European ancestry are all within the same linkage disequilibrium block spanning the *UMOD* promoter.[44] The ancestral alleles of these *UMOD* SNPs have allele frequencies of approximately 80% in the 1000G among persons of European ancestry (CEU). These variants include rs4293393 (A/G), rs12917707 (G/T), rs12922822 (C/T), rs13333226 (A/G), and rs13329952 (T/C).[44] The squared correlation (r^2) between these variants ranges from 0.91 to 1.0 for the 1000G CEU population (Supplementary Figure S1).

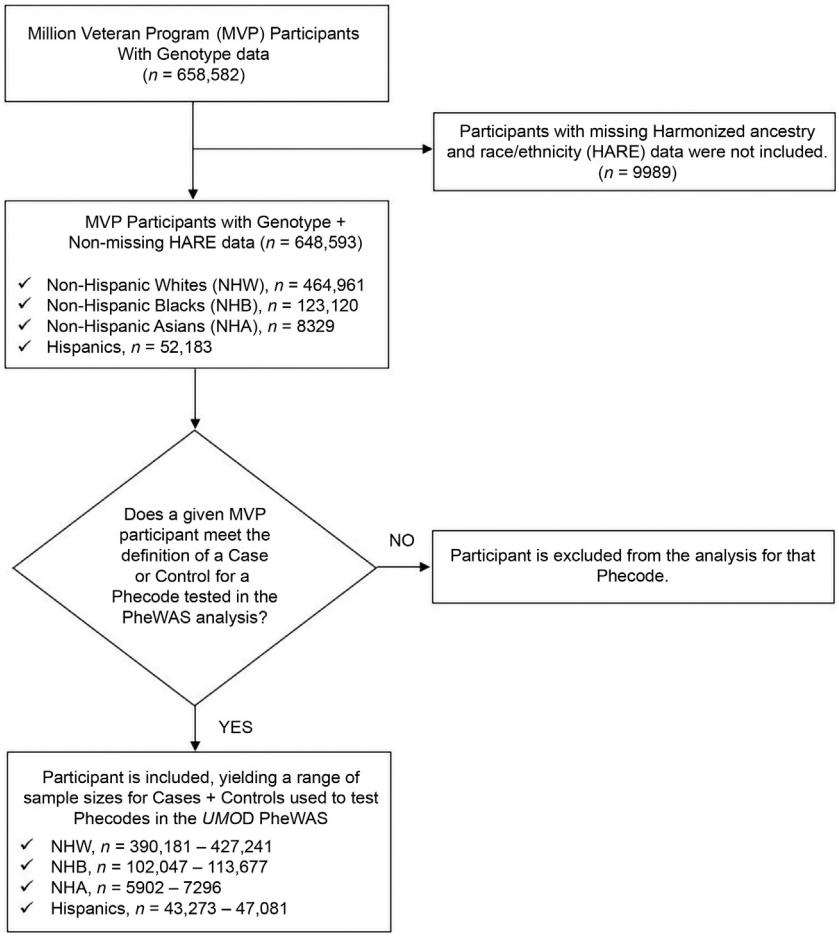

Figure 1. Flowchart for MVP Participants included in the UMOD PheWAS. HARE, harmonized ancestry and race/ethnicity; MVP, Million Veteran Program; PheWAS, phenome-wide association study.

The linkage disequilibrium patterns of *UMOD* variants in 1000G African Americans (Supplementary Figure S2), 1000G Mexican ancestry (Supplementary Figure S3), and 1000G Han Chinese individuals (Supplementary Figure S4) are considerably different to that in 1000G CEU, but the frequencies of the major alleles are all >70%. We also investigated the effects of *PDILT* (upstream of the *UMOD* locus) variants, including rs12446492 (T/A), rs77924615 (G/A), and rs11864909 (C/T), that have been reported in GWAS of renal traits.

Definition of Outcomes for PheWAS Analysis in the MVP

In the MVP, the outcomes for the PheWAS analysis were clinical phenotypes (phecodes) derived from International Classification of Disease, ninth revision (ICD-9) and International Classification of Disease, tenth revision (ICD-10) diagnosis codes.[45] ICD-9–based phenotypes were defined by mapping ICD-9 codes occurring in the EHR of patients to PheWAS codes, as previously described by Denny *et al.*[26,46] Meanwhile, ICD-10 codes were first mapped to ICD-9 codes using a crosswalk and then subsequently mapped to the phecodes. Additional information on the mapping between phecodes and both ICD-9 and ICD-10 codes (including exclusion phecodes for each phecode) are publicly available at: https://phewascatalog.org/phecodes and https://phewascatalog.org/phecodes_icd10.

As described in previous studies, for each phenotype, a patient was defined as being a case if they had ≥2 phecodes on 2 different dates.[46] Meanwhile, controls for the phenotype in question were individuals who had no phecodes for that phenotype and did not have phecodes for related phenotypes for that disease grouping (exclusion phecodes).[26,46] Furthermore, individuals with 1 phecode for a given phenotype were not considered a case or a control and were thus excluded from the analysis for that specific phenotype (Figure 1). A list of all phecodes tested in the MVP is included in Supplementary Table S1.

Statistical Methods for PheWAS Analysis in the MVP

Clinical phenotypes with fewer than 200 cases were excluded *a priori* from the analysis given that ORs for rare events are unreliable.[47] After these exclusions, the

number of phenotypes available for PheWAS analyses in non-Hispanic White, White female, White male, Black, Asian, and Hispanic patients was 1528, 853, 1439, 1237, 256, and 930, respectively.

In each population, the primary analyses were conducted using the rs4293393 *UMOD* and rs77924615 *PDILT* variants as predictor variables. For each variant, a batch of logistic regression models (1 per phenotype totaling 256 to 1528 depending on the number of phecodes meeting the *a priori* criteria for a given population) was fit to investigate the association with clinical phenotypes. All models were adjusted for age, sex (except for sex-stratified analysis), and 10 principal components.

ORs (95% CI) for significant SNP-phenotype associations were reported. Bonferroni correction (0.05/number of phenotypes tested) was used to correct for multiple testing. Hence, statistical significance was defined as a P value $< 0.05/1528$ (or 3.27×10^{-05}) for non-Hispanic White patients. Similarly, the thresholds for statistical significance in non-Hispanic Black, Hispanic, Asian, White female, and White male patients were 4.04×10^{-05}, 5.38×10^{-05}, 1.95×10^{-04}, 5.86×10^{-05}, and 3.47×10^{-05}, respectively. In White female patients, we also reported ORs for phenotypes at a nominal significance level of 5.0×10^{-03} considering the smaller sample. We investigated variant-and-sex and variant-and-ancestry interactions by leveraging the difference in the stratum-specific log ORs and their variances to perform 2-sample Z-tests of interaction assuming asymptotic normality of the test statistics for large samples, as described elsewhere.[48,49] P interaction < 0.05 was considered significant.

In sensitivity analyses, the PheWAS analyses were repeated using the other *UMOD*/*PDILT* variants (in high linkage disequilibrium with SNPs used in the primary analyses) to assess the consistency of the findings. In MVP, all *UMOD*/*PDILT* variants used in the PheWAS were either directly genotyped or imputed with imputation quality (Supplementary Table S2). All analyses were performed using the R PheWAS package.

Replication Cohorts

Replication of the MVP PheWAS results was conducted in the Vanderbilt University Medical Center biorepository (BioVU) and the UK Biobank.

The BioVU resource is a DNA biobank at Vanderbilt University Medical Center linked to the synthetic derivative, a deidentified mirror image of their EHR containing inpatient and outpatient data with a goal to investigate links between genetics and health outcomes.[50] The BioVU replication was performed using individual-level data for 77,550 individuals who were genotyped on the Infinium Multiethnic Genotyping Array (MEGAchip). Details have been published elsewhere.[50] Excluded DNA samples were those with per-individual call rate $< 95\%$, wrongly assigned sex, cryptic relatedness closer than a third-degree relative, or unexpected duplication. Whole genome imputation was performed using the Michigan Imputation Server with the Haplotype Reference Consortium version r1.1 as reference. The list of phecodes tested in BioVU is listed in Supplementary Table S1.

The UK Biobank is a prospective cohort study of the effects of genetic, lifestyle, and environmental factors on disease outcomes. The study recruited >500,000 volunteers from the general population of the United Kingdom aged 40 to 69 years from 2006 to 2010.[51] Details have been published elsewhere.[51] Briefly, the phenotypes available in the UK Biobank are derived from diverse sources, including ICD-10 codes. Although Supplementary Table S1 lists the phecodes tested in the UK Biobank, there were 178 phenotypes tested in MVP that were not tested in the UK Biobank (Supplementary Table S3).

Replication Analyses in BioVU and UK Biobank

Clinical phenotypes that had significant associations with the candidate *UMOD*/*PDILT* variants in MVP were further evaluated in the BioVU repository. In BioVU, the *UMOD*/*PDILT* variants used in the PheWAS were also directly genotyped or imputed with high imputation quality (Supplementary Table S4). PheWAS regression analysis was performed adjusting for age, sex, 10 principal components, and length of EHR. For the replication studies, a less conservative nominal significance level was chosen, $P < 0.05$. All analyses for the BioVU data were performed on Vanderbilt's Computing cluster.

For White British participants in the UK Biobank, data for clinical phenotypes associated with a given genetic variant including P values and number of samples per phenotype are available online at pheweb.org/UKB-SAIGE/. PheWAS analyses were conducted using SAIGE (a generalized mixed model), adjusting for genetic relatedness, sex, birth year, and the first 4 principal components.

RESULTS

The mean (SD) age of the 648,593 MVP participants included in this *UMOD* PheWAS was 62 (14) years; 9% were female, 19% Black, 8% Hispanic, and 1.3% Asian. Table 1 illustrates the frequency of clinical phenotypes captured using phecodes. Hypertension and type 2 diabetes were common with case frequencies ranging from 62.8 to 74.7 and 35.1 to 43.5, respectively, across population groups. Supplementary Table S5 illustrates

the characteristics of non-Hispanic White ($n = 63,029$) and non-Hispanic Black patients ($n = 14,521$) who were included in the BioVU replication. The proportion of female patients was 56% and 62%, respectively, in both groups, and the mean (SD) age was 57 (22) and 47 (21) years. Supplementary Table S6 illustrates the population characteristics of the UK Biobank participants. The mean age was 56 (8) years, 54.4% were female, 27.1% had hypertension, and >5.3% had self-reported diabetes.

In MVP, among non-Hispanic White patients, the MAFs of the rs4293393 and rs77924615 variants were 18% and 20%, respectively (Supplementary Table S7). The corresponding MAFs for these variants in non-Hispanic Black patients were 21% and 6%. In Hispanic and non-Hispanic Asian patients, the MAFs for these variants were 21% and 20% and 10% and 20%, respectively.

PheWAS of *UMOD* and *PDILT* Variants in Non-Hispanic Whites—Discovery and Replication

In non-Hispanic White patients, the rs4293393 *UMOD* promoter variant was significantly associated with 29 clinical phenotypes at the 3.27×10^{-05} threshold (Table 2).

Each copy of the A allele of rs4293393 (that correlates with increased Umod expression) was associated with a significant 22% higher odds (OR: 1.22, 95% CI: 1.20–1.24) of CKD, 11% higher odds (OR: 1.11; 95% CI: 1.08–1.13) of diabetic kidney disease, 17% higher odds (OR: 1.17, 95% CI: 1.17–1.24) of end-stage kidney disease, and 6% higher odds (OR: 1.06, 95% CI: 1.04–1.09) of acute kidney injury (AKI). The A allele of rs4293393 was also associated with increased odds of proteinuria (OR: 1.10, 95% CI: 1.05–1.14), anemia of CKD (OR: 1.20, 95% CI: 1.14–1.25), secondary hyperparathyroidism of renal origin (OR: 1.21, 95% CI: 1.14–1.21), hypertension (OR: 1.03, 95% CI: 1.02–1.05), hypertensive CKD (OR: 1.20, 95% CI: 1.17–1.22), hypertensive heart or renal disease (OR: 1.10, 95% CI: 1.09–1.12), hyperkalemia (OR: 1.07, 95% CI: 1.04–1.10), and gout (OR: 1.04, 95% CI: 1.02–1.06). Conversely, the A allele of rs4293393 was significantly associated with lower odds of UTI (OR: 0.94, 95% CI: 0.92–0.96), urinary calculus (OR: 0.85, 95% CI: 0.83–0.86), calculus of the kidney (OR: 0.83, 95% CI: 0.81–0.85), calculus of the ureter (OR: 0.81, 95% CI: 0.78–0.84), and hematuria (OR: 0.95, 95% CI: 0.93–0.97). These findings were consistent with those observed for the other primary analysis using the rs77924615 *PDILT* variant (Figure 2a and b) and further confirmed in supplementary analyses using other *UMOD* promoter and *PDILT* variants (Supplementary Tables S8–S13 and Supplementary Table S5).

Overall, the findings for most of these clinical phenotypes were replicated in the UK Biobank and/or BioVU at $\alpha = 0.05$ (Table 2 and Supplementary Tables S14 and S15). For example, in BioVU, the OR (95% CI) per copy of the A allele of rs4293393 for calculus of the kidney, UTI, and CKD stage 3 was 0.85 (95% CI: 0.79–0.92, $P = 4.02 \times 10^{-05}$), 0.94 (95% CI: 0.90–0.98, $P = 1.00 \times 10^{-02}$), and 1.13 (95% CI: 1.05–1.22, $P = 1.5 \times 10^{-03}$), respectively.

PheWAS of *UMOD/PDILT* Variants in Non-Hispanic Black Patients

In Black patients, there were significant differences in the patterns of association between clinical phenotypes and both *UMOD* promoter variants (rs4293393 and rs12917707) and the *PDILT* variant (77924615; Figure 2c and 2d). The rs77924615 *PDILT* variant was significantly associated with phenotypes in 4 domains of interest (CKD, hypertension, calculus, and UTI). Each copy of the G allele of the rs77924615 variant was associated with increased odds of CKD stage III (OR: 1.15, 95% CI: 1.08–1.23, $P = 2.27 \times 10^{-05}$) and hypertensive CKD (OR: 1.15, 95% CI: 1.08–1.22, $P = 2.78 \times 10^{-06}$) and lower odds of urinary calculus (OR: 0.82, 95% CI: 0.76–0.89, $P = 1.68 \times 10^{-06}$), calculus of the kidney (OR: 0.81, 95% CI: 0.74–0.89, $P = 4.52 \times 10^{-06}$), and pyelonephritis (OR: 0.65, 95% CI: 0.54–0.79, $P = 1.05 \times 10^{-05}$) (Figure 2). However, no phenome-wide significant associations were observed between the rs4293392 *UMOD* promoter variant and any of the 4 domains of clinical phenotypes observed in non-Hispanic White patients, despite the number of cases for these phenotypes varying between 5323 and 87,895 (Table 3). The *P* values for differential effects between non-Hispanic White and Black patients for the association of the rs4293393 *UMOD* promoter variant and the 4 domains of clinical phenotypes observed in non-Hispanic Whites were 1.47×10^{-25} for CKD, 1.59×10^{-02} for hypertension, 2.15×10^{-05} for UTI, and 2.35×10^{-05} for urinary calculus (Supplementary Table S16). For the rs12917707 *UMOD* promoter variant, the G allele was significantly associated with 18% lower odds (OR: 0.82, 95% CI: 0.76–0.89, $P = 6.0 \times 10^{-06}$) of urinary calculus (Supplementary Table S5).

PheWAS of *UMOD* and *PDILT* Variants in Hispanic and Non-Hispanic Asian Patients

In Hispanic patients, both *UMOD* promoter and *PDILT* variants had phenome-wide significant associations with renal phenotypes that were observed among non-Hispanic White patients. For example, each copy of the A allele of the rs4293393 *UMOD* promoter variant was associated with increased odds of CKD (OR: 1.15, 95% CI:

Table 2. Significant associations of the rs4293393 (A/G) *UMOD* variant with clinical phenotypes among non-Hispanic White patients in the Million Veteran Program and Replication results from BioVU (Vanderbilt's Biobank) and UK Biobank

	Million Veteran Program					Replication cohorts	
Clinical phenotypes	PheWAS code description	Cases	Controls	OR (95% CI) per copy of the A allele	*P* value	BioVU	UK Biobank
Increased risk							
CKD	CKD	56,757	354,568	1.22 (1.20–1.24)	5.90×10^{-111}	Yes[a]	Yes
	CKD, stages I–II	8236	411,510	1.11 (1.07–1.19)	3.29×10^{-05}	No[b]	No
	CKD, stage III	37,099	379,128	1.24 (1.21–1.26)	2.79×10^{-86}	Yes	No
	CKD, stage IV	8918	416,152	1.23 (1.19–1.29)	1.33×10^{-23}	Yes	No
Diabetic kidney disease	Type 2 diabetes with renal manifestations	21,706	395,843	1.11 (1.08–1.13)	2.76×10^{-14}	No	No
Proteinuria	Proteinuria	9030	411,051	1.10 (1.05–1.14)	4.31×10^{-06}	Yes	No
End-stage kidney disease and related disorders	End-stage renal disease	5334	421,018	1.17 (1.11–1.24)	2.40×10^{-09}	No	Yes
	Renal failure, NOS	5950	415,270	1.16 (1.10–1.22)	4.20×10^{-09}	No	Yes
	Secondary hyperparathyroidism of renal origin	4716	421,292	1.21 (1.14–1.28)	1.69×10^{-11}	No	No
	Anemia of CKD	7330	416,175	1.20 (1.14–1.25)	7.31×10^{-15}	No	Yes
	Disorders resulting from impaired renal function	6104	418,597	1.17 (1.12–1.23)	1.79×10^{-10}	No	No
Acute kidney injury	Acute renal failure	37,825	367,058	1.06 (1.04–1.09)	5.50×10^{-10}	No	Yes
Electrolyte imbalance	Electrolyte imbalance	51,136	338, 927	1.04 (1.02–1.05)	2.33×10^{-05}	No	No
Hyperkalemia	Hyperpotassemia	15,510	395,633	1.07 (1.04–1.10)	2.62×10^{-05}	No	Yes
Hypertension and complications	Hypertension	303,313	102,754	1.03 (1.02–1.05)	2.11×10^{-06}	No	Yes
	Essential hypertension	301,525	104,191	1.03 (1.02–1.05)	3.08×10^{-06}	No	Yes
	Hypertensive CKD	30,565	381,368	1.20 (1.17–1.22)	1.89×10^{-53}	No	Yes
	Hypertensive heart or renal disease	53,251	346,382	1.10 (1.09–1.12)	5.11×10^{-29}	No	Yes
Gout	Gout	38,796	379,147	1.04 (1.02–1.06)	1.94×10^{-05}	Yes	No
Anemia	Anemia of chronic disease	13,675	403,118	1.13 (1.09–1.16)	9.05×10^{-13}	No	No
	Other anemias	76,540	313,641	1.03 (1.02–1.05)	2.00×10^{-05}	No	Yes
Decreased risk							
UTIs	UTI	42,133	351,924	0.94 (0.92–0.96)	1.21×10^{-10}	Yes	No
Urinary calculi	Urinary calculus	36,238	376,038	0.85 (0.83–0.86)	1.45×10^{-64}	Yes	Yes
	Calculus of the kidney	30,249	383,255	0.83 (0.81–0.85)	4.27×10^{-69}	Yes	Yes
	Calculus of the ureter	8817	413,932	0.81 (0.78–0.84)	1.77×10^{-29}	Yes	Yes
	Calculus of the lower urinary tract	2784	423,008	0.81 (0.76–0.87)	4.93×10^{-10}	No	Yes
	Hydronephrosis	6559	415,441	0.88 (0.84–0.92)	9.20×10^{-09}	No	Yes
Hematuria	Hematuria	36,418	368,018	0.95 (0.93–0.97)	4.40×10^{-07}	No	Yes
	Gross hematuria	12,904	405, 647	0.94 (0.91–0.97)	3.26×10^{-05}	No	No

BioVU, biorepository; CKD, chronic kidney disease; NOS, not otherwise specified; OR, odds ratio; PheWAS, phenome-wide association study; UTI, urinary tract infection.
[a]Yes means that the association was replicated in BioVU or the UK Biobank.
[b]No means that the association was not replicated in BioVU or the UK Biobank.
All associations listed were significant at the Bonferroni-corrected significance level of 3.27×10^{-05}.

1.09–1.22, $P = 7.10 \times 10^{-07}$) and hypertensive CKD (OR: 1.16, 95% CI: 1.08–1.24, $P = 4.27 \times 10^{-05}$) and lower odds of calculus of the kidney (OR: 0.84; 95% CI: 0.79–0.90, $P = 1.55 \times 10^{-07}$; Supplementary Figure S6). These effect estimates were similar for the rs12917707 *UMOD* promoter variant and the rs77924615 *PDILT* variant (Supplementary Table S5). However, no significant association was observed with UTI despite a considerable number of observed cases, $n = 4428$ (Supplementary Tables S17 and S18). In non-Hispanic Asian patients, no phenome-wide significant phenotypes were observed for the rs4293393 *UMOD* promoter variant. However, for the rs77924615 *PDILT* variant, 1 phenotype namely CKD stage III (OR: 1.90, 95% CI: 1.34–2.04, $P = 3.25 \times 10^{-5}$) reached phenome-wide significance.

Sex Differences in the PheWAS of *UMOD* and *PDILT* Variants in Non-Hispanic White Patients

In non-Hispanic White male patients, the findings for the *UMOD* promoter and *PDILT* variants were consistent with the patterns observed in the total pool of non-Hispanic White patients with similar effect sizes and *P* values (Figure 3c and d). In White female patients, there were 3 clinical phenotypes reaching phenome-wide significance for the rs77924615 *PDILT* variant and 2 for the *UMOD* promoter variants

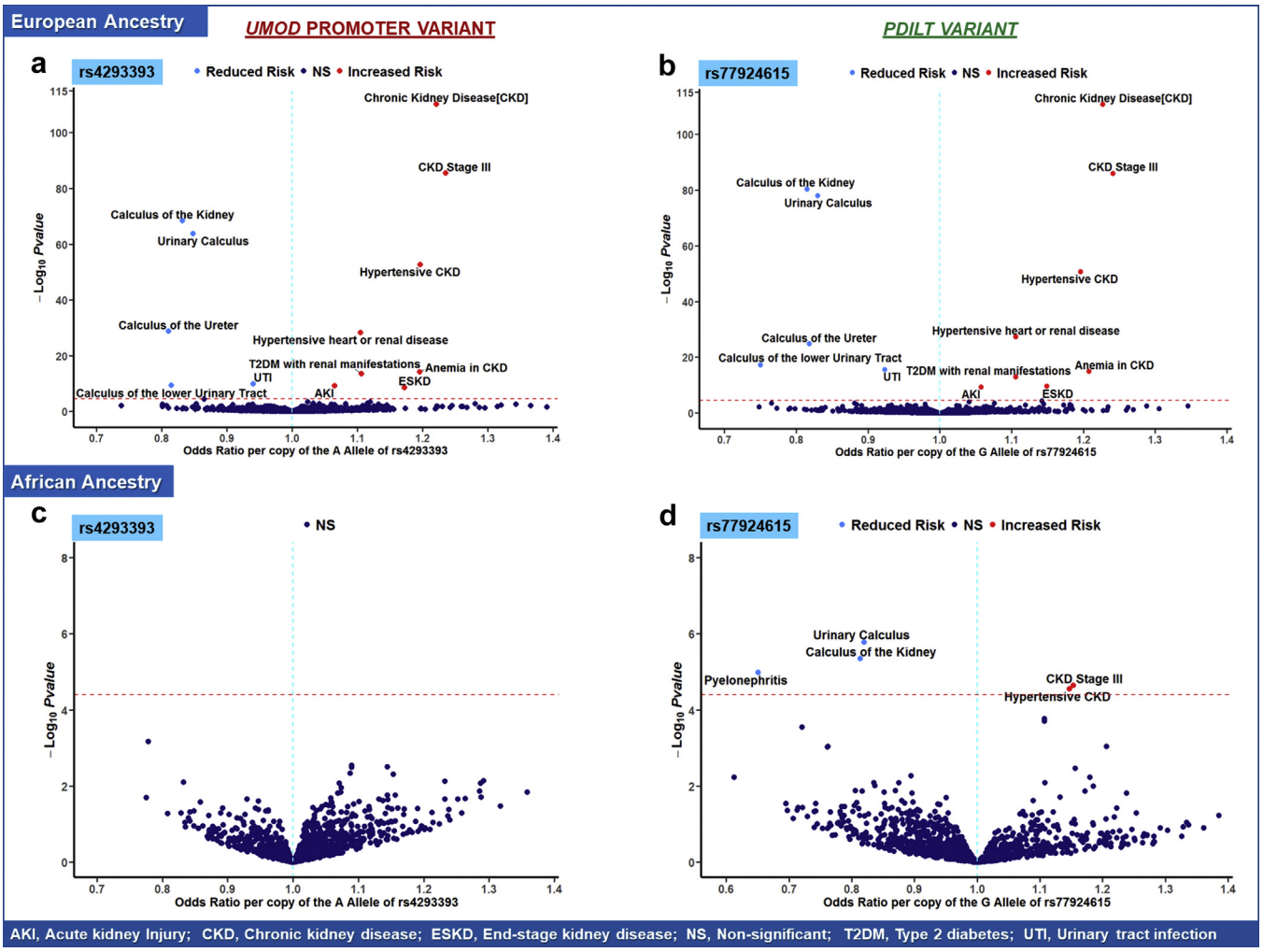

Figure 2. Volcano plot illustrating key clinical phenotypes significantly associated with *UMOD* promoter (rs4293393) and *PDILT* variants (rs77924615) in (a, b) non-Hispanic White and (c, d) non-Hispanic Black patients in the Million Veteran Program. In each plot, the red line indicates the significance threshold for Bonferroni correction as a reference. Phenotypes in the right upper quadrant have increased odds per copy of the allele associated with increased Umod expression, whereas phenotypes in the left quadrant have decreased odds. In Black patients, no significant variant-phenotype associations were observed for the rs4293393 *UMOD* promoter variant. Five significant variant-phenotype associations were observed for the *PDILT* variant rs4293393. In White patients, a wide range of significant variant-phenotype associations were observed corroborating the pleiotropic effects of Umod on human physiology. In addition, there were no noticeable differences in the patterns of variant-phenotype associations between *UMOD* promoter and *PDILT* variants. AKI, acute kidney injury; CKD, chronic kidney disease; ESKD, end-stage kidney disease; NS, nonsignificant; T2DM, type 2 diabetes mellitus; UTI, urinary tract infection.

rs12917707 and rs4293393 (Figure 3a and b). For example, each copy of the A allele of the rs4293393 variant was associated with 27% increased odds of CKD (OR: 1.27, 95% CI: 1.14–1.40) and 19% lower odds (OR: 0.81, 95% CI: 0.74–0.88) of calculus of the kidney (Table 4). Six other phenotypes reached nominal significance ($\alpha = 5 \times 10^{-3}$), specifically hypertensive CKD, hypertensive heart or renal disease, CKD stage 3, elevated white blood cell count, urinary calculus, and calculus of the ureter. Overall, the difference in effect sizes for these phenotypes was minimal between the sexes. However, for acute cystitis, the effect was considerably stronger among White female patients with an OR (95% CI) per copy of the G allele of the rs77924615 *PDILT* variant of 0.73 (95% CI: 0.59–0.91, $P = 4.98 \times 10^{-03}$) compared with 0.99 (95% CI: 0.89–1.11, $P = 8.80 \times 10^{-01}$) among White male patients (P interaction = 0.01) (Supplementary Tables S16 and S19). The G allele of the rs77924615 variant was associated with increased odds of heart failure with preserved ejection fraction (OR: 1.28, 95% CI: 1.09–1.50, $P = 3.01 \times 10^{-03}$) among White female patients. Among White male patients, the effect estimate was 1.00 (95% CI: 0.97–1.03, $P = 0.89$).

DISCUSSION

In this PheWAS of common *UMOD*/*PDILT* gene variants using data from large multiethnic biobanks, we report significant associations of *UMOD* risk variants

Table 3. Effect estimates in non-Hispanic Blacks for clinical phenotypes that were significantly associated with the rs4293393 (A/G) *UMOD* variant in non-Hispanic White patients in the Million Veteran Program

	Million Veteran Program				
Clinical phenotypes	**PheWAS code description**	**Cases**	**Controls**	**OR (95% CI) per copy of the A allele**	***P* value**
CKD	CKD	19,540	90,000	1.02 (0.99–1.05)	1.14×10^{-01}
	CKD, stages I–II	4583	106,035	1.03 (0.98–1.09)	2.61×10^{-01}
	CKD, stage III	11,929	99,163	1.03 (0.99–1.07)	9.57×10^{-02}
	CKD, stage IV	3953	109,453	1.06 (1.00–1.12)	4.58×10^{-02}
Diabetic kidney disease	Type 2 diabetes with renal manifestations	8393	102,371	1.01 (0.97–1.05)	7.76×10^{-01}
Proteinuria	Proteinuria	4357	106,600	1.02 (0.96–1.07)	5.38×10^{-01}
End-stage kidney disease and related disorders	End-stage kidney disease	3873	109,875	1.04 (0.98–1.10)	1.91×10^{-01}
	Renal failure, NOS	3205	108,717	1.02 (0.96–1.08)	5.82×10^{-01}
	Secondary hyperparathyroidism of renal origin	2860	110,654	1.03 (0.96–1.10)	3.92×10^{-01}
	Anemia of CKD	4347	108,345	1.04 (0.98–1.04)	2.00×10^{-01}
	Disorders resulting from impaired renal function	3478	109,570	1.02 (0.97–1.09)	3.57×10^{-01}
Acute kidney injury	Acute renal failure	13,954	92,382	1.01 (0.98–1.05)	3.90×10^{-01}
Electrolyte imbalance	Electrolyte imbalance	17,004	86,178	1.01 (0.98–1.04)	4.66×10^{-01}
Hyperkalemia	Hyperpotassemia	4517	105,759	1.05 (1.00–1.11)	4.94×10^{-02}
Hypertension and complications	Hypertension	87,895	21,857	0.99 (0.96–1.02)	6.96×10^{-01}
	Essential hypertension	87,503	22,156	0.99 (0.97–1.02)	7.26×10^{-01}
	Hypertensive CKD	12,633	96,524	1.03 (1.00–1.06)	7.60×10^{-02}
	Hypertensive heart or renal disease	19,685	86,457	1.03 (1.00–1.06)	3.68×10^{-02}
Gout	Gout	13,193	97,948	1.02 (0.98–1.05)	3.62×10^{-01}
Anemia	Anemia of chronic disease	6641	103,775	1.03 (0.98–1.05)	3.62×10^{-01}
	Other anemias	29,742	73,176	1.01 (0.98–1.03)	5.57×10^{-01}
UTIs	UTI	13,886	88,161	1.02 (0.98–1.05)	2.45×10^{-01}
Urinary calculi	Urinary calculus	5323	105,846	0.95 (0.90–0.99)	2.49×10^{-02}
	Calculus of the kidney	4435	107,159	0.95 (0.91–1.01)	7.83×10^{-01}
	Calculus of the ureter	1201	112,536	0.91 (0.83–1.01)	6.87×10^{-01}
	Calculus of the lower urinary tract	394	113,757	0.91 (0.77–1.07)	2.59×10^{-01}
	Hydronephrosis	1354	111,996	0.94 (0.86–1.03)	2.18×10^{-01}
Hematuria	Hematuria	11,005	95,973	1.02 (0.98–1.05)	3.52×10^{-01}
	Gross hematuria	3922	107,820	1.04 (0.98–1.10)	2.08×10^{-01}

CKD, chronic kidney disease; NOS, not otherwise specified; OR, odds ratio; PheWAS, phenome-wide association study.

with increased risk of CKD and hypertension and lower risk of UTIs and kidney stones. Importantly, we observed differential patterns in the pleiotropic effects of *UMOD* risk variants on clinical phenotypes related to Umod physiology across ancestry groups, which have not been previously reported.

In non-Hispanic White patients, there were consistent SNP-phenotype associations across *UMOD* promoter and *PDILT* variants. *UMOD* promoter and *PDILT* risk variants (alleles associated with increased Umod expression) were significantly associated with increased risk of kidney disease phenotypes (CKD, diabetic kidney disease, and end-stage kidney disease), hypertension, and complications of hypertension (hypertensive heart or renal disease) while being protective for UTIs and urolithiasis. Conversely, in Black patients, clear differences in SNP-phenotype associations were observed between variants in the *UMOD* promoter and *PDILT* locus with variants in the latter having significant effects with the aforementioned Umod-related phenotypes. In particular, the rs77924615 *PDILT* variant had strong protective effects for pyelonephritis. The variant-phenotype associations in Hispanic patients were mostly consistent with those observed in non-Hispanic White patients but the associations with UTIs were null (ORs close to 1) raising potential questions regarding the causal variants in Hispanic patients and the genetic architecture of UTIs in this population. The findings in non-Hispanic Asian patients revealed a particularly strong association of the rs77924615 variant with CKD stage 3 (90% increased odds per copy of the G allele that increases Umod expression) despite a null effect for the rs4293393 *UMOD* promoter variant. The fact that these patterns are in clear contrast with those observed in non-Hispanic White patients suggests the needed for additional investigation into differential patterns in Asian versus European ancestry populations using larger samples in future studies. Sex differences in the ORs for the aforementioned phenotypes were minimal except for stronger effects of the rs7724615 *PDILT* variant on acute cystitis and heart failure with

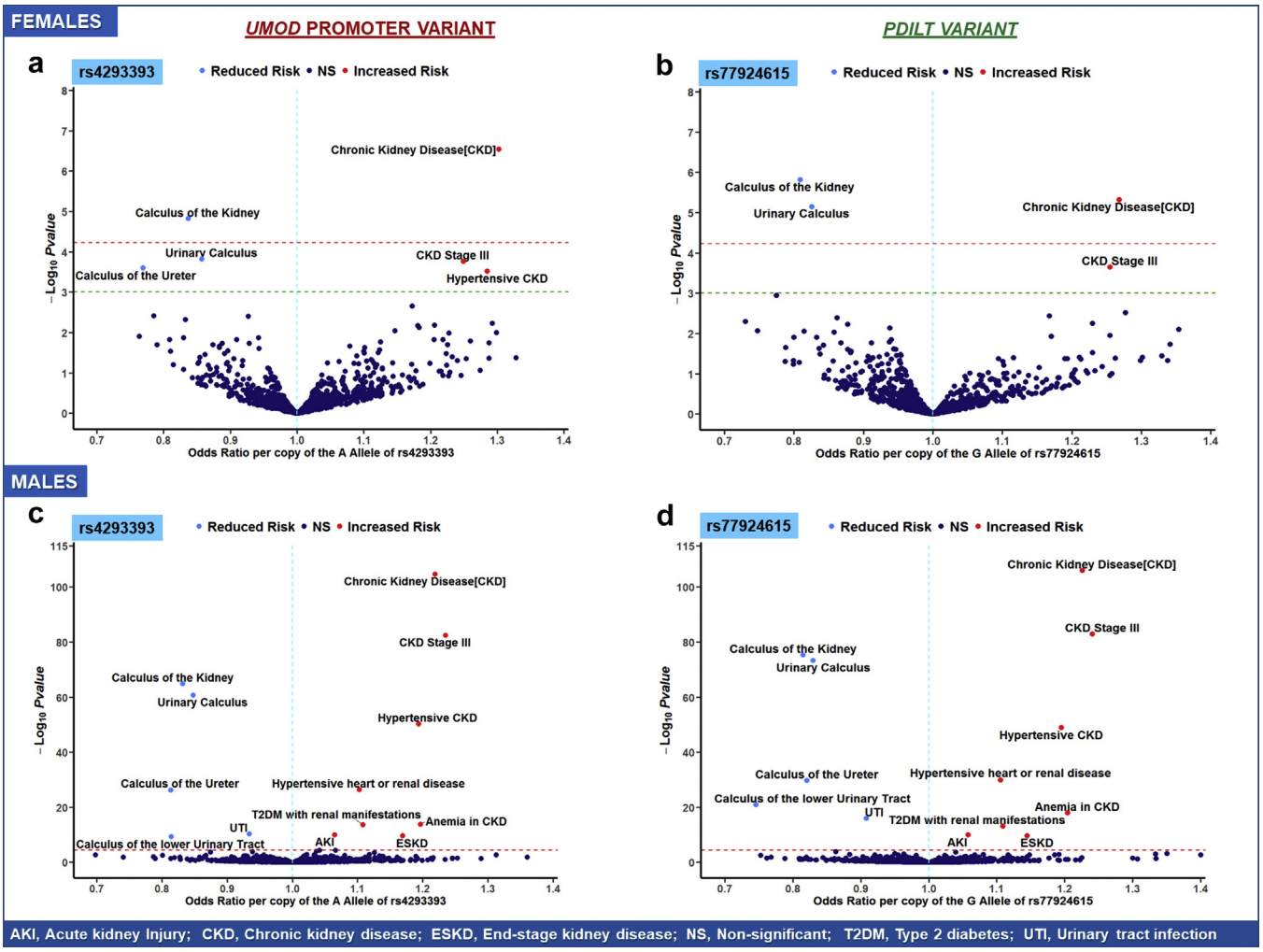

Figure 3. Volcano plot illustrating key clinical phenotypes significantly associated with *UMOD* promoter (rs4293393) and *PDILT* variants (rs77924615) in non-Hispanic White female (a, b) and male (c, d) patients in the Million Veteran Program. In each plot, the red line indicates the significance threshold for Bonferroni correction as a reference whereas the green line indicates nominal significance at $\alpha = 5 \times 10^{-3}$. Phenotypes in the right upper quadrant have increased odds per copy of the allele associated with increased Umod expression, whereas phenotypes in the left quadrant have decreased odds. All clinical phenotypes typically associated with Umod expression had significant associations with *UMOD* promoter and *PDILT* variants in White male patients. In White female patients, significant variant-phenotype associations were observed for CKD, urinary calculus, and calculus of the kidney. Nominally significant associations were observed with acute cystitis and heart failure with preserved EF. AKI, acute kidney injury; CKD, chronic kidney disease; EF, ejection fraction; ESKD, end-stage kidney disease; NS, nonsignificant; T2DM, type 2 diabetes mellitus; UTI, urinary tract infection.

preserved ejection fraction in White female versus male patients which needs to be investigated further in future work.

Previous GWAS have established the association between common *UMOD* variants and CKD in cohorts from multiple populations, including European,[17,18] Icelandic,[52] and multiethnic.[21,53] Case-control data have also revealed significant associations with hypertension and incident cardiovascular disease independently of eGFR.[22] Our PheWAS findings extend these prior data by revealing significant associations with both early and advanced stages of CKD and both renal and cardiovascular complications of hypertension in clinical settings, for *UMOD* promoter risk variants among non-Hispanic White patients. Our findings corroborate those previously reported by Shang *et al.*[54] who found significant associations for the rs28544423 *UMOD* variant (in complete linkage disequilibrium with rs4293393) with CKD stage 3 in 78,638 European ancestry individuals in the eMERGE network. However, in our multiethnic PheWAS, these associations with CKD and hypertension and hypertensive complications were not observed for *UMOD* promoter risk variants in non-Hispanic Black patients. Notably, in a previous GWAS of kidney traits conducted exclusively in African Americans in the CARE consortium, the rs4293393 *UMOD* promoter variant did not have a significant association with CKD and urinary albumin-to-creatinine ratio and only reached nominal significance for eGFR.[55] These findings

Table 4. Association of the rs4293393 (A/G) *UMOD* variant with key clinical phenotypes across sex groups in non-Hispanic White patients in the MVP

Females					
Clinical phenotypes	**PheWAS code description**	**Cases**	**Controls**	**OR (95% CI) per copy of the A allele**	***P* value**
CKD	CKD	1685	28,924	1.30 (1.18–1.44)	2.87×10^{-07}[a]
	CKD, stage III	1154	29,725	1.25 (1.10–1.45)	2.39×10^{-04}
	CKD, stage IV	263	31,007	1.62 (1.24–2.11)	4.00×10^{-04}
Hypertensive complications	Hypertensive CKD	774	30,108	1.28 (1.11–1.49)	7.50×10^{-04}
	Hypertensive heart or renal disease	1567	28,773	1.17 (1.06–1.30)	2.20×10^{-03}
UTIs	UTI	7840	18,560	0.98 (0.98–1.05)	4.03×10^{-01}
	Cystitis	977	28,707	0.87 (0.78–0.98)	2.01×10^{-02}
	Acute cystitis	245	30,151	0.84 (0.68–1.05)	1.31×10^{-01}
	Pyelonephritis	584	30,061	0.92 (0.79–1.07)	2.62×10^{-01}
Urinary calculi	Urinary calculus	1990	28,328	0.86 (0.79–0.93)	1.73×10^{-04}
	Calculus of the kidney	1710	28,751	0.84 (0.77–0.91)	4.98×10^{-05}[a]
	Calculus of the ureter	518	30,514	0.77 (0.66–0.89)	5.37×10^{-04}
Males					
Clinical phenotypes	**PheWAS code description**	**Cases**	**Controls**	**OR (95% CI) per copy of the A allele**	***P* value**
CKD	CKD	55,072	325,644	1.22 (1.20–1.24)	2.09×10^{-105}[a]
	CKD, stage III	35,945	349,403	1.23 (1.21–1.26)	2.82×10^{-83}[a]
	CKD, stage IV	8655	385,145	1.23 (1.18–1.28)	1.54×10^{-21}[a]
Hypertension complications	Hypertensive chronic kidney disease	29,791	351,260	1.19 (1.17–1.22)	4.31×10^{-51}[a]
	Hypertensive heart or renal disease	51,684	317,609	1.10 (1.08–1.12)	3.68×10^{-27}[a]
UTIs	UTI	34,293	333,364	0.93 (0.92–0.95)	4.35×10^{-11}[a]
	Cystitis	3638	385,756	0.97 (0.92–1.03)	3.44×10^{-01}
	Acute cystitis	1096	391,828	0.92 (0.83–1.02)	1.26×10^{-01}
	Pyelonephritis	2232	391,619	0.91 (0.84–0.98)	9.18×10^{-03}
Urinary calculi	Urinary calculus	34,248	347,710	0.85 (0.83–0.86)	1.45×10^{-61}[a]
	Calculus of the kidney	28,539	354,504	0.83 (0.81–0.85)	4.20×10^{-65}[a]
	Calculus of the ureter	8299	383,418	0.81 (0.78–0.84)	5.22×10^{-27}[a]

CKD, chronic kidney disease; MVP, Million Veteran Program; OR, odds ratio; PheWAS, phenome-wide association study; UTI, urinary tract infection.
[a]Represents phenotypes reaching PheWAS significance among non-Hispanic White female (5.86×10^{-05}) and male patients (3.47×10^{-05}) in the MVP.

contrast with those from large multiethnic studies,[21,53] whose results are likely driven by the larger European cohorts in the meta-analysis. Our multiethnic PheWAS suggests differences in the effect of *UMOD* promoter risk variants on advanced CKD and hypertensive renal and/or heart disease between patients of European and African ancestry, and this observed heterogeneity in allelic effects for *UMOD* promoter risk variants is novel and may portend potential clinical relevance. Prior data from Trudu *et al.*[24] had established Umod as a potential therapeutic target for blood pressure lowering and nephroprotection. Trudu *et al.*[24] reported that increased Umod expression in transgenic mice led to salt-sensitive hypertension (owing to Umod-mediated hyperactivation of NKCC2 in the thick ascending limb) and the development of age-dependent lesions in the kidney that were similar to those observed in older patients that are homozygous for high-risk alleles of *UMOD* promoter variants, such as the carriers of the AA genotype of the rs4293393 variant reported in the current study. Trudu *et al.*[24] also reported that pharmacologic inhibition of the NKCC2 cotransporter using furosemide was more effective on blood pressure lowering in patients with hypertension who are homozygous for *UMOD* promoter risk variants than in other patients with hypertension revealing a link between genetic susceptibility to hypertension and CKD to Umod expression levels and Umod-mediated reabsorption of sodium chloride in the thick ascending limb. Devuyst *et al.*[44] thus highlighted a potential personalized medicine recommendation for furosemide which may be more efficacious in patients with hypertension who are homozygous for *UMOD* promoter risk variants. Our findings further extend this potential precision medicine recommendation by highlighting that the possible benefit of SNP-dependent furosemide effects may also be ancestry dependent. Although patients with hypertension of European ancestry who are homozygotes for *UMOD* promoter variants may have more potent furosemide effects, this may not be the case for patients of African ancestry. However, the observed effect of the rs77924615 *PDILT* variant on hypertensive CKD in patients of African ancestry does raise the question whether this variant maybe a better potential candidate—compared with the *UMOD* promoter variants—to explore for precision medicine approaches in this patient population.

The observed deleterious effects of *UMOD* risk variants on diabetic kidney disease and proteinuria in patients of European ancestry may be an important finding that is relevant to ongoing research on therapies for diabetic kidney disease. In future work, it may be of interest to investigate whether the presence of *UMOD* risk variants modifies the beneficial effect of nephroprotective drugs (RAAS inhibitors,[56,57] SGLT2 inhibitors,[58–62] and mineralocorticoid antagonists[63]) in diabetic patients. In our eGFR GWAS, the observed *UMOD* effect on kidney function was greater in patients with diabetes versus patients without diabetes.[18,64] The effect of extraluminal Umod may be attributed to the proximity of the thick ascending limb to the macula densa where Umod may interfere with the tubuloglomerular feedback increasing intraglomerular pressure.[65]

UMOD risk variants were also associated with increased AKI risk. The consistent findings across *UMOD* and *PDILT* variants and concurrent significant signals with accompanying signs of AKI such as hyperkalemia provide some corroboration to the observed UMOD-AKI association. However, this association may have been confounded by underlying CKD especially given that previous studies have suggested Umod as a potentially useful biomarker in models of AKI with higher levels being associated with better prognosis.[66,67]

The observed protective effects of the major alleles of the *UMOD* variants on nephrolithiasis and UTIs in this study among individuals of European ancestry corroborate previous data.[11–13,68–70] Umod's propensity to reduce kidney stone formation has been linked to its sialylated negatively charged glycans that inhibit aggregation of calcium oxalate and calcium phosphate crystals.[70,71] Meanwhile, although Umod has been known to protect against UTIs by binding uropathogenic *Escherichia coli*,[12,72] the precise mechanism was poorly understood until the landmark paper by Weiss *et al*.[73] They revealed that the Umod filament consists of a zigzag-shaped backbone with laterally protruding arms. Specifically, Umod acts as a multivalent ligand for FimH on the bacterial pili, presenting several specific glycan epitopes which outcompete glycan receptors on the urothelium.[11,73] Several Umod-uropathogen interactions occur between the multiple binding sites of the Umod filament and several pili on the bacterium causing bacterial aggregation and preventing attachment to the urothelium and clearance by micturition.[73]

In Black patients, no protective effects on urolithiasis were observed for the major allele of the rs4293393 *UMOD* promoter variant. These effects were observed for the rs12917707 and rs77924615 variants. The latter also had a strong protective effect on pyelonephritis. Similarly, in White female patients, stronger effects were observed for the rs77924615 *PDILT* variant on acute cystitis compared with *UMOD* promoter variants. In a transethnic eGFR GWAS in >1 million individuals, Wuttke *et al*.[21] found that the rs77924615 *PDILT* variant had a strong causal regulatory role on the *UMOD* gene and Umod expression in the kidney by extension. This strong regulatory role of the rs77924615 variant on uromodulin production and urinary uromodulin levels may explain its greater effect on UTIs in female patients.

The strengths of our study include the large sample of patients with available genetic data, racial/ethnic diversity, and the presence of long follow-up time in the EHR, which increases the potential to capture clinical phenotypes using diagnostic codes. In addition, the Veterans Affairs is a closed health care system where patients have continuity of care which further minimizes ascertainment bias for patient outcomes. Furthermore, although the primary findings were obtained using MVP data, a replication phase was conducted in BioVU and the UK Biobank. Several limitations exist including the exclusive utilization of diagnostic codes to define outcomes. However, Cai *et al*.[45] revealed PPVs of 80% to 100% for major cardiovascular phenotypes in their PheWAS of IL6R variants in the MVP. Requiring at least 2 codes to ascertain a case for each phenotype in our study reduces false positives. Furthermore, eliminating "uncertain" cases from the case-control pool makes the comparison groups more biologically disparate and likely increases the signal-to-noise ratio in this study. Moreover, assuming any potential outcome misclassification may likely be nondifferential across alleles of the *UMOD* variants; the ORs would be, at worst, biased toward the null. Dense phenotyping information on study outcomes (e.g., information on bacteriology for UTIs and antibiotic treatments) would have facilitated more in-depth analyses. However, as these extraneous factors are unlikely to have different distributions across alleles of the *UMOD* variants (which are antecedent by definition), they are unlikely to confound the ORs reported in this study. The absence of data on urinary uromodulin levels to supplement the reported genetic effects is another limitation. Although the PheWAS analyses in non-Hispanic White and Black patients were adequately powered for the main findings (Supplementary Table S20), our analysis in Hispanic patients (Supplementary Table S21) and non-Hispanic White female patients was limited by lower statistical power.

In summary, we found significant associations between *UMOD*/*PDILT* risk variants linked with

increased Umod expression and increased risk of CKD and hypertension and lower odds of UTIs and nephrolithiasis. However, these associations varied significantly across ancestry groups and sex.

Implications

Using a PheWAS approach in multiethnic biobanks, we have highlighted significant heterogeneity in the pleiotropic effects of increased Umod expression on human disease between population groups—differences that may portend future relevance to personalized medicine for patients from diverse populations.

DISCLOSURE

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AUTHOR CONTRIBUTIONS

Study design: AMH and EAA. Data acquisition: AMH and CMS. Data analysis and interpretation: EAA, HC, GL, ZH, AG, QF, RT, AMH. Drafting of the manuscript: EAA. Critical revision of the manuscript for intellectual content: HC, CPC, AG, CR, TAI, CMS, EDS, QF, RT, AMH. All authors approve the final version of the manuscript.

SUPPLEMENTARY MATERIAL

Supplementary File (Word)

Figure S1. Linkage disequilibrium patterns between *UMOD* promoter and *PDILT* variants among individuals of European ancestry (CEU) in the 1000 Genomes reference panel.

Figure S2. Linkage disequilibrium patterns between *UMOD* promoter and *PDILT* variants among African Americans (ASW) in the 1000 Genomes reference panel.

Figure S3. Linkage disequilibrium patterns between *UMOD* promoter and *PDILT* variants among individuals of Mexican ancestry (MXL) in the 1000 Genomes reference panel.

Figure S4. Linkage disequilibrium patterns between UMOD promoter and PDILT variants among individuals of Han Chinese ancestry (CHB) in the 1000 Genomes reference panel.

Figure S5. Volcano plot showing clinical phenotypes significantly associated with the rs4293393 *UMOD* promoter and rs77924614 *PDILT* variants in non-Hispanic Asian and Hispanic patients in the Million Veteran Program.

Figure S6. Volcano plot illustrating key clinical phenotypes significantly associated with the rs12917707 *UMOD* promoter in the 4 populations (non-Hispanic White, non-Hispanic Black, non-Hispanic Asian, and Hispanic patients) in the Million Veteran Program.

Table S1. List of Phecodes tested in MVP and BioVU participants.

Table S2. Imputation quality scores (R2) for *UMOD/PDILT* variants in MVP.

Table S3. List of Phecodes that were tested in MVP but not in the UK Biobank.

Table S4. Imputation quality scores (R2) for *UMOD/PDILT* variants in BioVU and UK Biobank participants.
Table S5. Characteristics of BioVU (Vanderbilt's Biobank) participants that were included in the *UMOD* PheWAS.
Table S6. Baseline characteristics of UK Biobank participants (n = 502,650).
Table S7. Allele frequencies of *UMOD* and *PDILT* variants across population groups in the Million Veteran Program.
Table S8. Association of the rs12917707 (G/T) *UMOD* promoter variant with clinical phenotypes that were significant in the primary analysis using the rs4293393 (A/G) *UMOD* promoter variant in non-Hispanic White patients in the MVP.
Table S9. Association of the rs12922822 (C/T) *UMOD* promoter variant with clinical phenotypes that were significant in the primary analysis using the rs4293393 (A/G) *UMOD* promoter variant in non-Hispanic White patients in the MVP.
Table S10. Association of the rs13333226 (A/G) *UMOD* promoter variant with clinical phenotypes that were significant in the primary analysis using the rs4293393 (A/G) *UMOD* promoter variant in non-Hispanic White patients in the MVP.
Table S11. Association of the rs13329952 (T/C) *UMOD* promoter variant with clinical phenotypes that were significant in the primary analysis using the rs4293393 (A/G) *UMOD* promoter variant in non-Hispanic White patients in the MVP.
Table S12. Association of the rs12446492 (T/A) *PDILT* variant with clinical phenotypes that were significant in the primary analysis using the rs77924615 (G/A) *PDILT* variant in non-Hispanic White patients in the MVP.
Table S13. Association of the rs11864909 (C/T) *PDILT* variant with clinical phenotypes that were significant in the primary analysis using the rs77924615 (G/A) *PDILT* variant in non-Hispanic White patients in the MVP.
Table S14. Effect estimates in BioVU participants for the association of the rs4293393 (A/G) UMOD promoter variant with clinical phenotypes that were significant in MVP non-Hispanic White patients.
Table S15. Effect estimates in UK Biobank participants for the association of the rs4293393 (A/G) UMOD promoter variant with clinical phenotypes that were significant in MVP non-Hispanic White patients.
Table S16. *P* values for the test of differential effects of the rs4293393 (A/G) UMOD variant on key clinical phenotypes in non-Hispanic White versus Non-Hispanic Black patients in the Million Veteran Program.
Table S17. Association of the rs4293393 (A/G) *UMOD* variant with UTIs across population groups in the Million Veteran Program.
Table S18. Association of the rs77924615 (G/A) *PDILT* Variant with UTIs across population groups in the Million Veteran Program.
Table S19. Association of the rs77924615 (G/A) *PDILT* variant with key clinical phenotypes across sex groups in the Million Veteran Program.
Table S20. Power estimates for the association between the rs4293393 *UMOD* variant and key clinical phenotypes in non-Hispanic White and Black patients.
Table S21. Power estimates for the association between the *UMOD/PDILT* variants and key clinical phenotypes in Hispanic patients.
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