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Association of rare variants in kidney developmental genes with hypertension and CKD: a UK Biobank study

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Disclosures

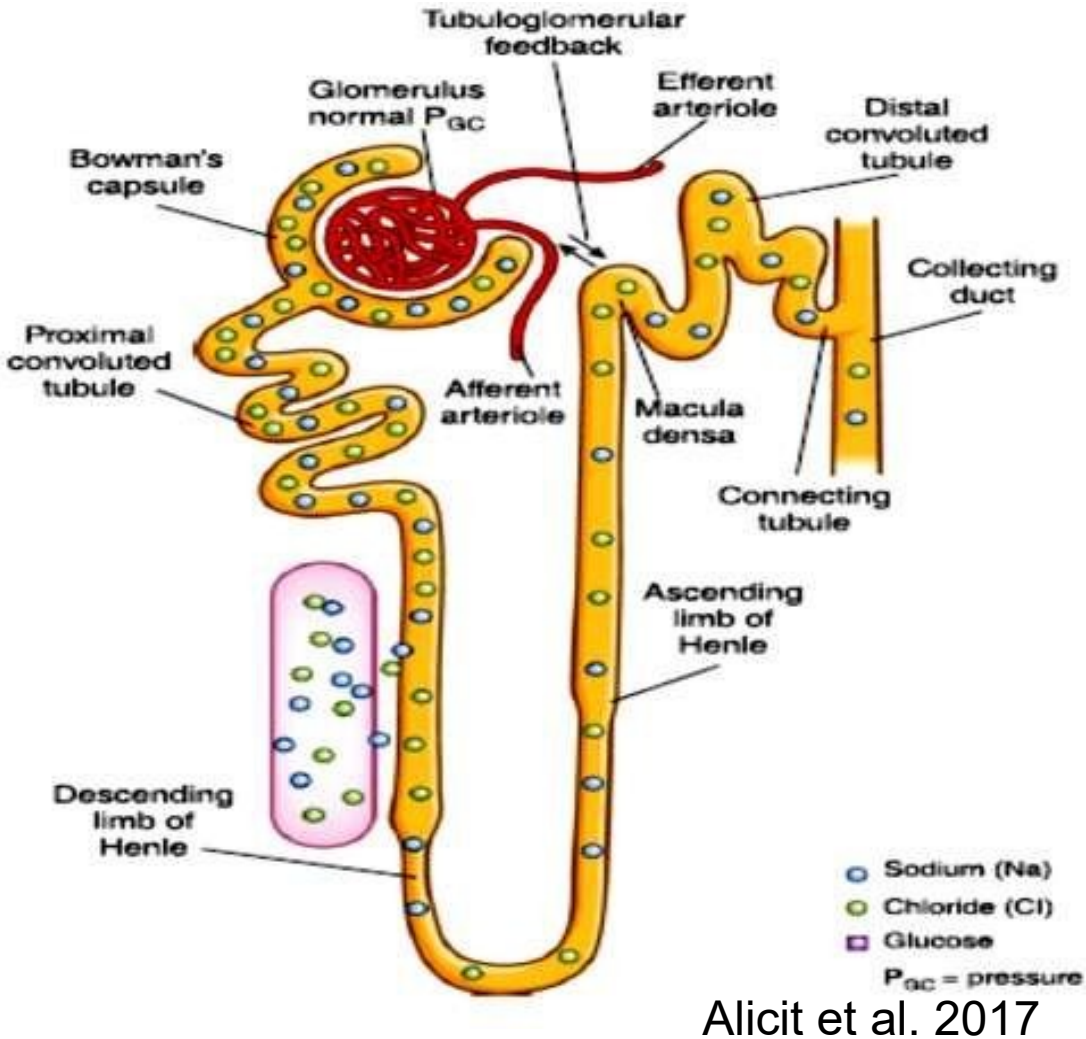
- No relevant conflicts of interest to disclose

Relationship of CKD and HTN

- Hypertension and chronic kidney disease (CKD) are interrelated diseases
- Hypertension is often a sequela of CKD due to impaired renal perfusion and RAAS activation
- Conversely, poorly controlled hypertension can cause glomerular hyperfiltration, resulting in development of CKD

Nephron endowment

- Total nephron number (nephron endowment) is inversely correlated with risk of kidney disease and hypertension
- There is variability in nephron endowment by race



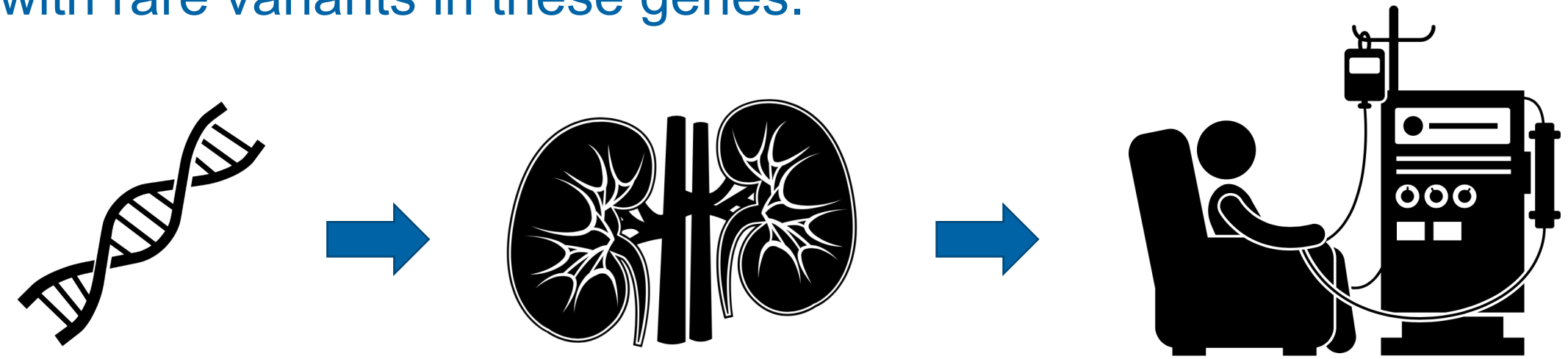
Alicit et al. 2017

Heritability of CKD and HTN

- The estimated heritability of CKD is ~30%
- Heritability of blood pressure is 20-60%
- Most studies examining source of this heritability have been large GWA studies examining common variants (e.g., MAF >10%)
- Common variants have only identified a small proportion of the heritability in these traits

Hypothesis

- Rare variants in genes implicated in nephrogenesis result in abnormal nephron development (i.e. decreased nephron endowment) increasing risk of CKD and BP elevation in individuals with rare variants in these genes.



Methods

49,989 volunteers, age 40-69 years with whole exome sequencing (WES)

58 renal developmental genes in 5 developmental compartments:
- Early nephron development
- Podocytes
- Tubulointerstitial cells
- Collecting duct
- Endothelium

Identified presence of qualifying variant in each gene:
- MAF <0.1% AND
- ACMG classification "pathogenic", "likely pathogenic", or "uncertain significance"

CKD covariates:
- Diabetes mellitus
- Elevated BP
- Vascular heart disease

Logistic regression model for each developmental compartment examining qualifying variants ability to predict CKD and HTN, with subgroup analysis by genetic ethnicity

Elevated BP covariates:
- Diabetes mellitus
- Vascular heart disease
- Hyperlipidemia
- Overweight
- Smoking status

Results- Blood Pressure

	All			Caucasian			Non-Caucasian		
Compartment	**Gene**	**OR (99% CI)**	**P**	**Gene**	**OR (99% CI)**	**P**	**Gene**	**OR (99% CI)**	**P**
Early nephron development	*SIX1*	0.574 (0.349-0.941)	0.004	*SIX1*	0.583 (0.342-0.992)	0.009	*WT1*	2.494 (1.076-5.778)	0.005
	WT1	1.581 (1.018-2.453)	0.007	-	-	-	-	-	-
Podocytes	*NPHS1*	0.843 (0.719-0.987)	0.005	-	-	-	-	-	-

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	WT1	1.581 (1.018-2.453)	0.007	-	-	-	-	-	-
Podocytes	*NPHS1*	0.843 (0.719-0.987)	0.005	-	-	-	-	-	-

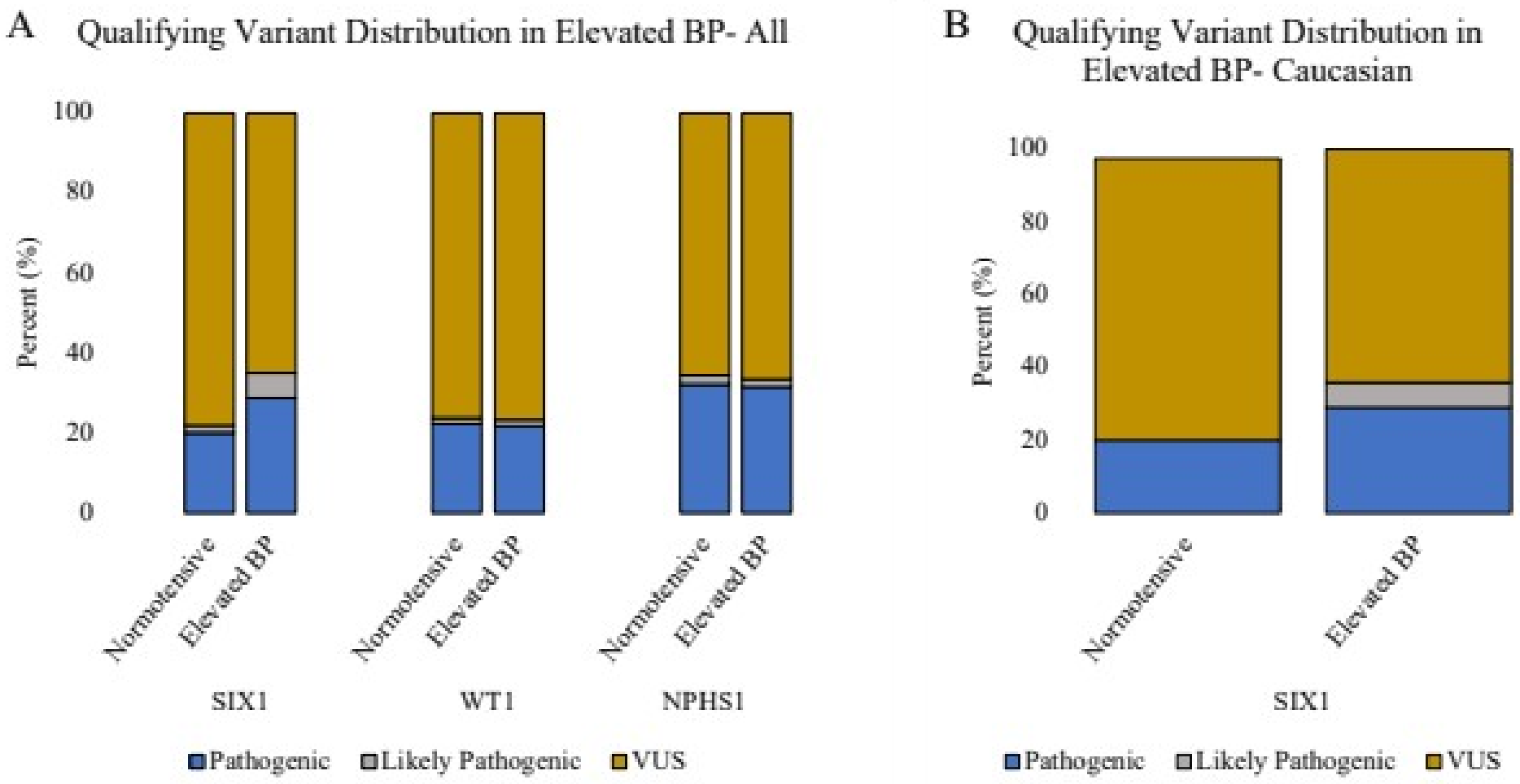
Results- CKD

	All			Caucasian			Non-Caucasian		
Compartment	**Gene**	**OR (99% CI)**	**P**	**Gene**	**OR (99% CI)**	**P**	**Gene**	**OR (99% CI)**	**P**
Tubulointerstitial cells	*CLCN5*	1.588 (1.022-2.469)	0.007	-	-	-	*SLC12A3*	2.020 (1.081-3.776)	0.004
Collecting duct	-	-	-	-	-	-	*CALB1*	3.119 (1.149-8.468)	0.003

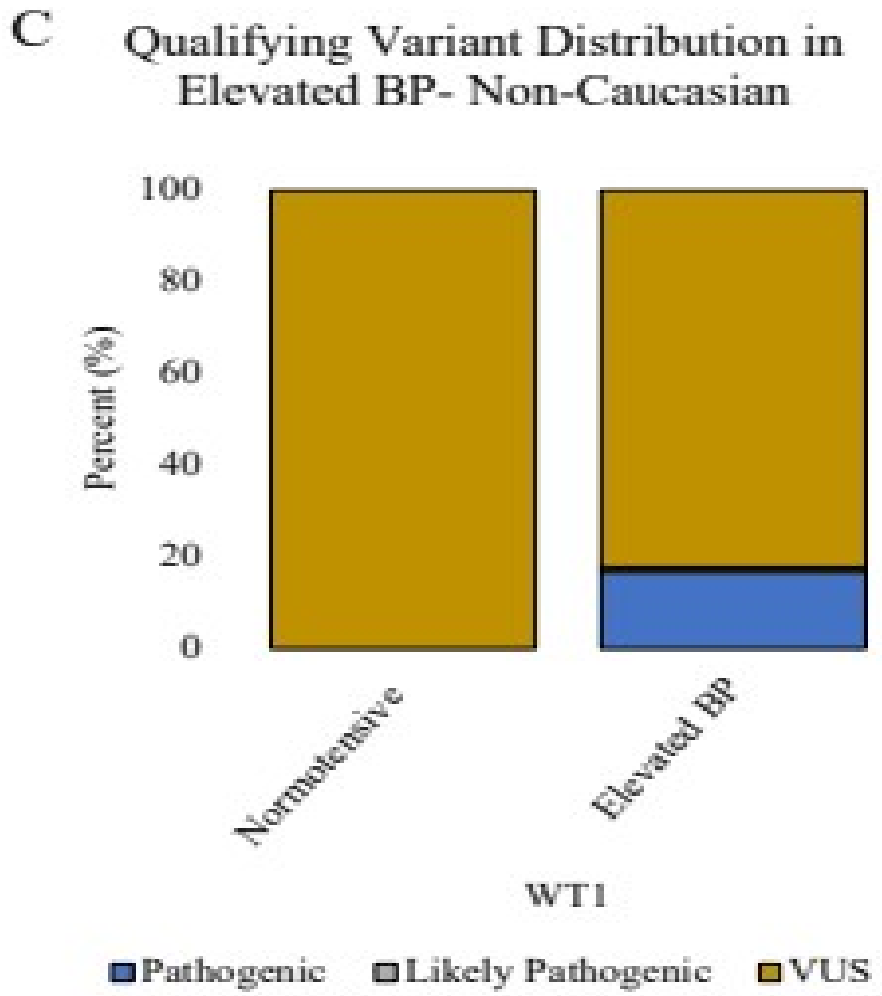
Potential reasons for protective vs deleterious associations

- Definition of qualifying variants

Distribution of qualifying variant by ACMG category



Qualifying variant distribution by ACMG category



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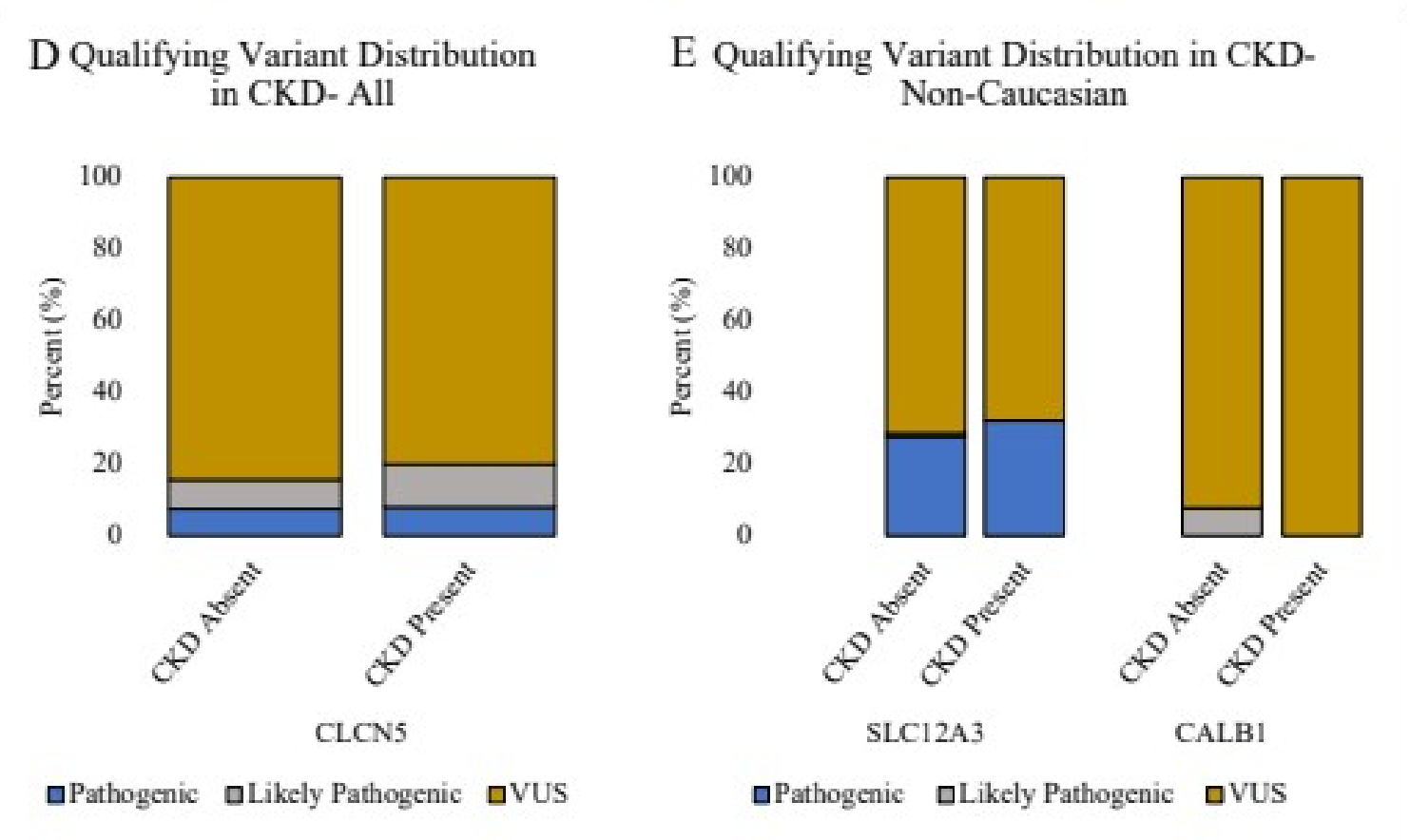
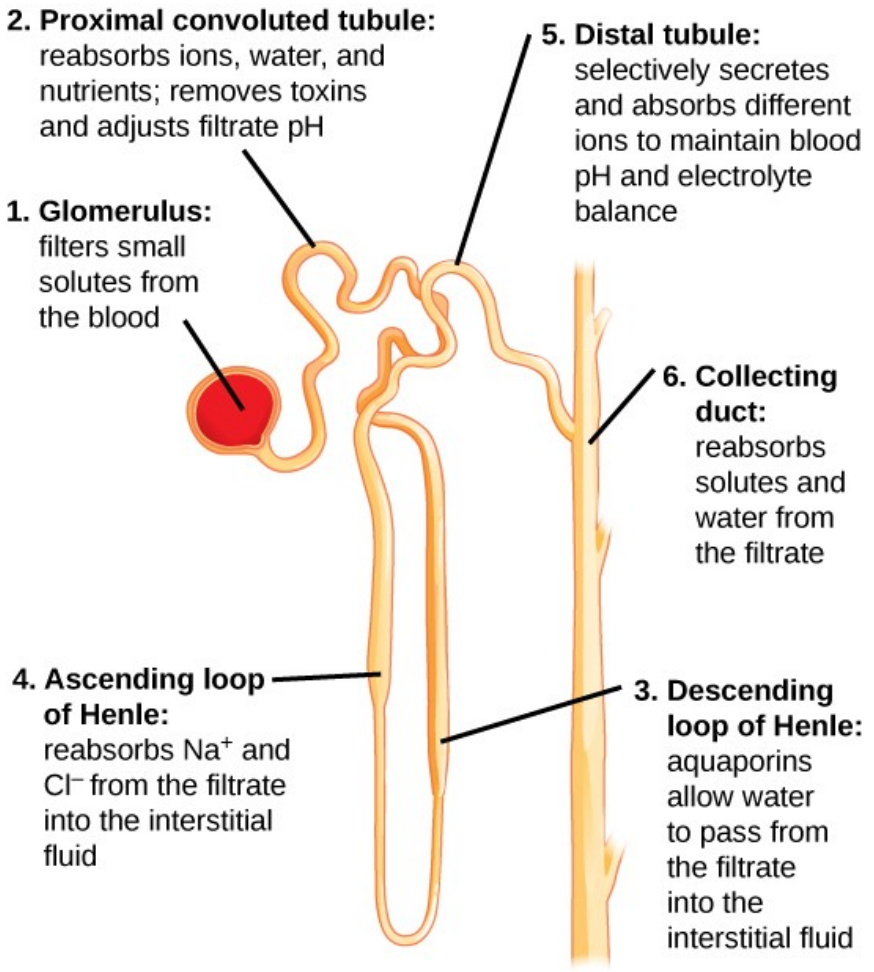


Potential reasons for protective vs deleterious associations

- Definition of qualifying variants
- Renal physiology

Could these findings be attributable to impaired salt handling?

- Could impairment of tubules/collecting duct cause inability to concentrate urine and/or reabsorb sodium leading to hypotension?
- Supported by Ji *et al.* demonstrating that rare variants in the salt handling genes *SLC12A3*, *SLC12A1*, and *KCNJ1*(*ROMK*) were associated with reduced blood pressure



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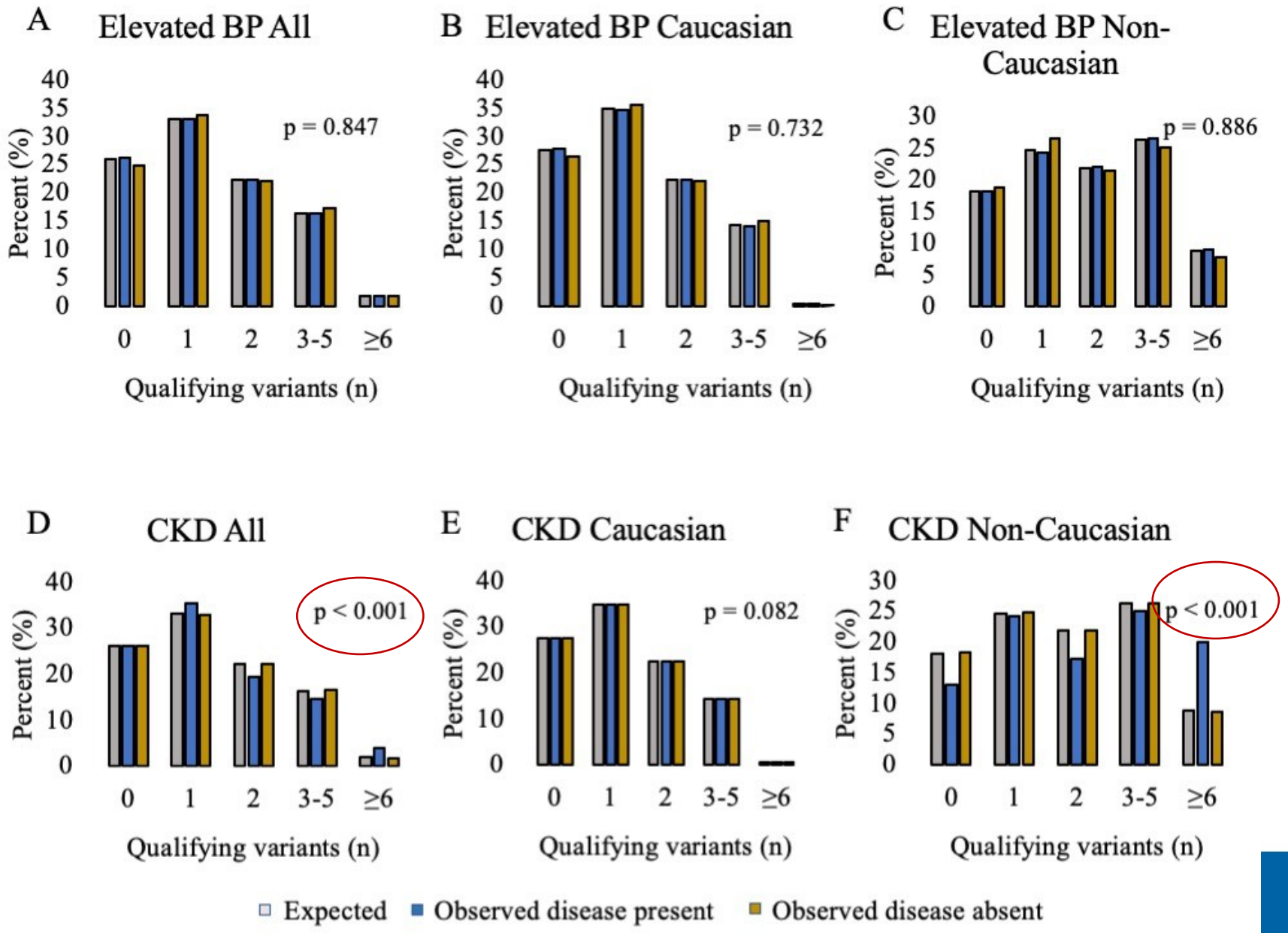
Does qualifying variant count differ in CKD and HTN?

Qualifying variant distribution



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Individuals with CKD tend to have higher numbers of qualifying variants

- Relative to expected distribution, a higher proportion of individuals with CKD have large number of qualifying variants
  - Seen when evaluating whole cohort and in non-Caucasian subgroup

Reasons for ethnic discrepancy

- Misclassification of variants as “rare” due to admixed nature of “non-Caucasian” group
- Capturing rare variants that predispose some non-Caucasian subgroups to HTN and CKD

Conclusion

- Very rare variants in certain renal developmental genes are predictive of CKD and blood pressure (positively and negatively)
- Presence of very rare variants explain a proportion of the missing heritability of CKD and blood pressure
- Genes in which rare variants predict outcomes of interest vary by ethnicity

Future directions

- Assess for linkage disequilibrium of multiple variants within the same gene
- Assess impact of multiple qualifying variants on CKD/ blood pressure risk through development of genewise risk score.
- Rerun analyses on larger cohort

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Thank you!

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