4-2022

Rare variants in renal developmental genes and the risk of hypertension and CKD: a UK Biobank study

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Rare variants in renal developmental genes and the risk of hypertension and CKD: a UK Biobank study

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Background

- Hypertension and chronic kidney disease (CKD) are heritable traits.
- The source of this heritability is largely unknown.
- Studies exploring this missing heritability have principally focused on common genetic variants.

Objectives

- Identify rare genetic variants in renal developmental genes associated with hypertension and CKD.

Methods

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

58 kidney developmental genes:
- Early nephron development
- Podocytes
- Tubulointerstitial cells
- Collecting duct
- Endothelial cells

Qualifying variants:
- Minor allele frequency <0.1%
- Pathogenic, likely pathogenic, or variant of uncertain significance (VUS)

Logistic regression models for qualifying variants with CKD and blood pressure (BP)

Results

Table 1: Statistically significant predictors of BP

	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	-	-	-	-	-	-

Table 2: Statistically significant predictors of 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

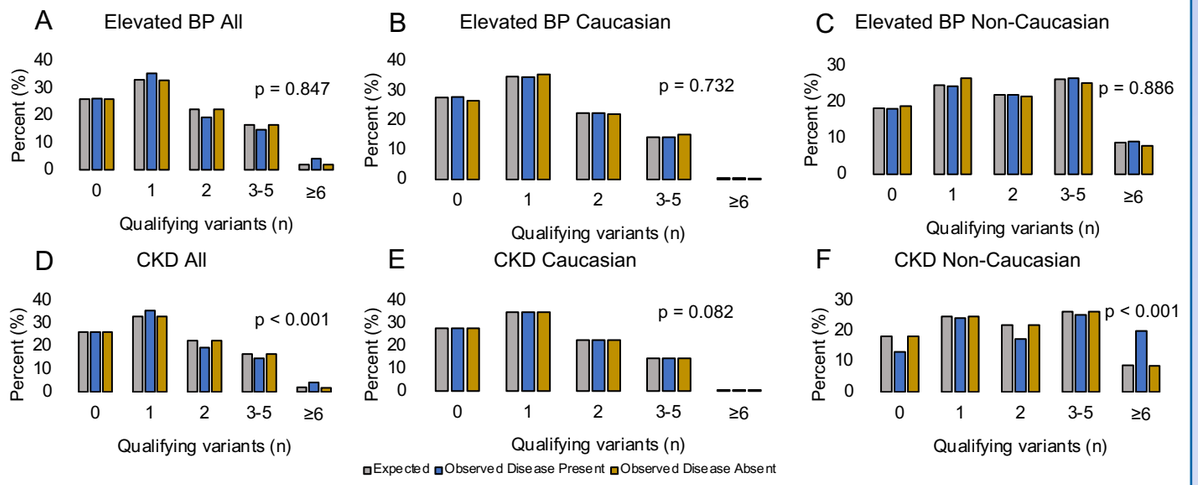

Figure 1: In the entire cohort and non-Caucasian subgroup, the proportion of individuals carrying ≥6 qualifying variants with CKD was greater than expected (D, F).

Discussion

- Rare genetic variants explain a degree of the heritability in CKD and BP.
- Individuals with CKD carry higher numbers of qualifying variants than expected.
  - Potential for linkage disequilibrium or additive effects.
- Ethnic variability exists regarding genes predictive of disease, and number of variants carried.
  - Certain non-Caucasian populations are at higher risk of CKD and elevated BP.
  - Possibly misclassifying certain variants as rare given heterogeneity of non-Caucasian subgroup.

Conclusions

- Rare variants in kidney developmental genes explain a portion of the heritability of CKD and BP.
- Further studies are needed to validate associations in underrepresented populations at risk for kidney disease.

Future Directions

- Replicative studies in underrepresented populations.
- Further characterization of VUSs.
- Assessment linkage disequilibrium between qualifying variants.
- Development of a polygenic risk score assessing impact of multiple variants on CKD and elevated BP risk.

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