Supplemental Material

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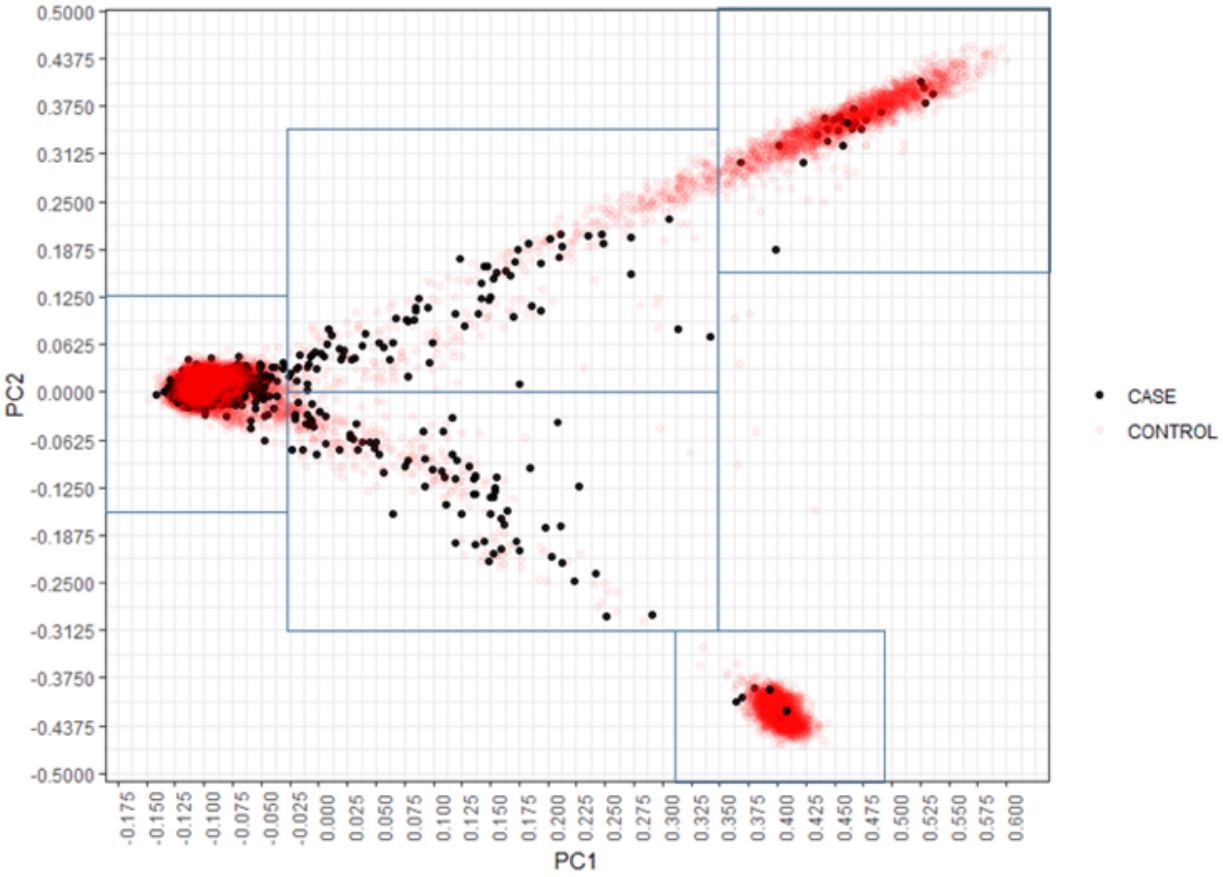
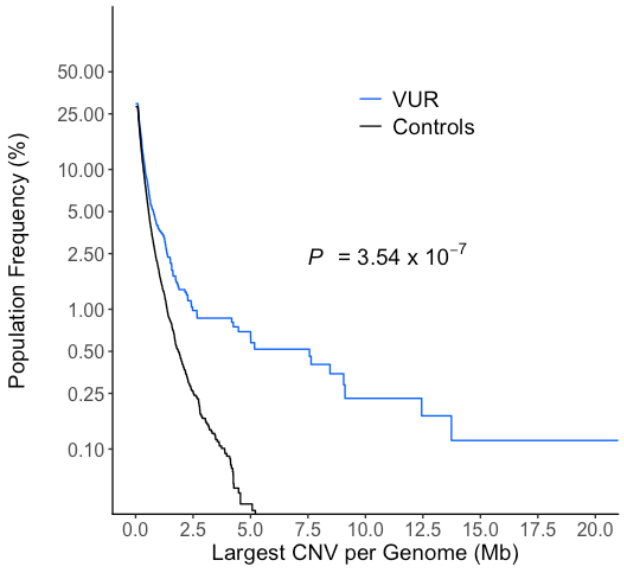


Supplemental Figure 1. Principal component analysis (PCA) for CNV frequency filtering. Boxes indicate five subpopulations of individuals used to filter CNVs for burden analysis. CNVs with a frequency in any one of these five subpopulations higher than 0.1% were filtered out. Six controls, outliers in PCA without matching cases, were removed prior to burden analyses. PC: Principal component.

Size threshold	VUR n = 1737	Controls n = 24,759	O.R. (95% C.I.)	*P*
100 kb	514 (29.59%)	6,970 (28.15%)	1.07 (0.96-1.19)	0.21
500 kb	145 (8.35%)	1,515 (6.12%)	1.40 (1.16-1.67)	3.96×10^{-4}
1,000 kb	66 (3.8%)	481 (1.94%)	1.99 (1.51-2.6)	1.8×10^{-6}
2,000 kb	24 (1.38%)	105 (0.42%)	3.29 (2.01-5.18)	3.12×10^{-6}

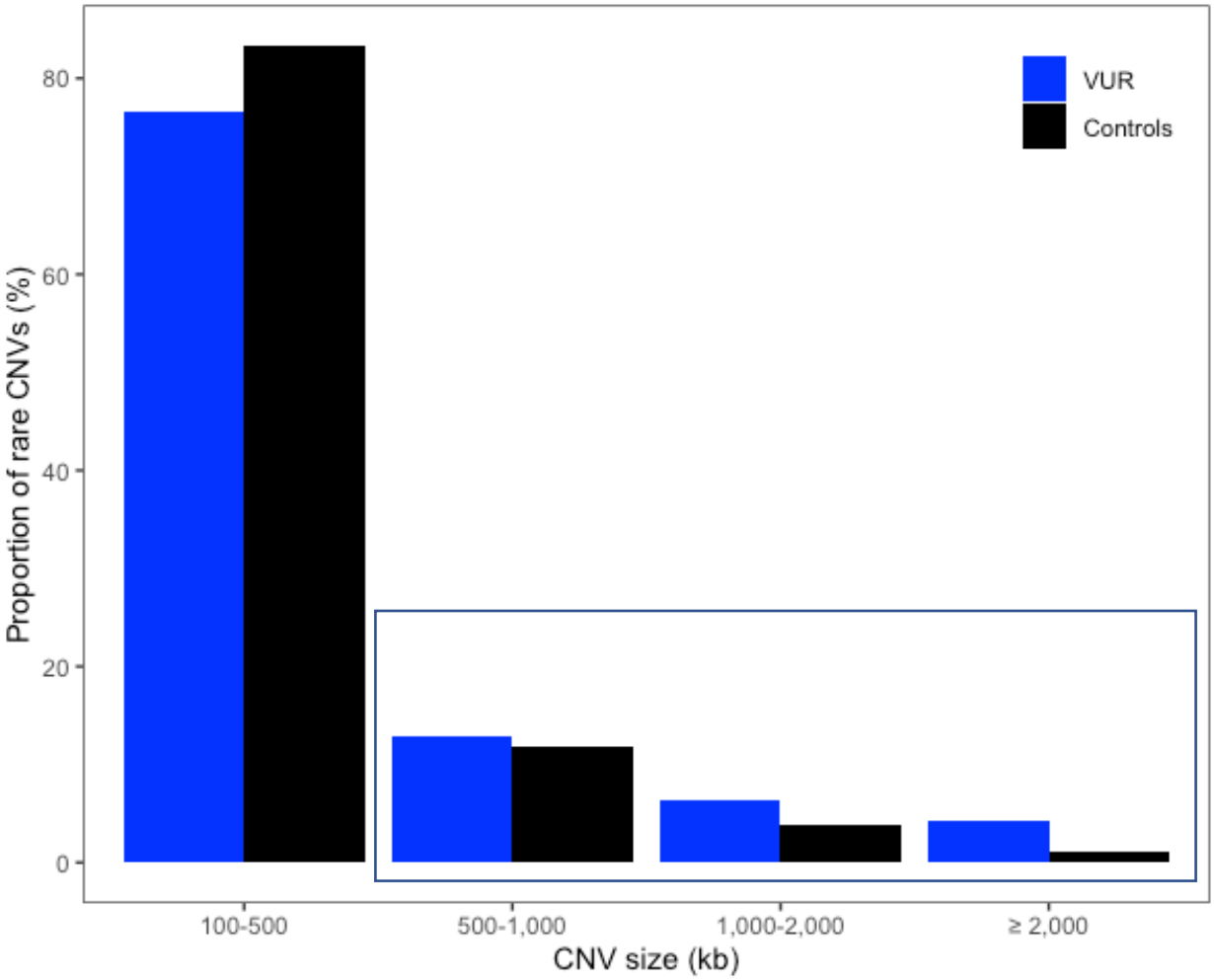
Supplemental Table 1. Excess burden of large, rare CNVs in VUR compared to controls.
Counts (%) of subjects with their largest rare (frequency in PCA-defined populations ≤ 0.1%), gene-intersecting CNV size at or above the indicated size thresholds (kb); Odds ratios (O.R.); their 95% confidence intervals (C.I.) and Fisher's Exact test *P*-values are tabulated.



Supplemental Figure 2. Excess burden of large, rare CNVs in VUR compared to controls
Large (size ≥ 100 kb), rare (frequency in PCA-defined populations ≤ 0.1%), gene-intersecting CNV burden as a survival function of the largest CNV per genome show excess burden in VUR cases (blue line) compared to controls (black line). Log-rank test P-value = 3.54×10^{-7}

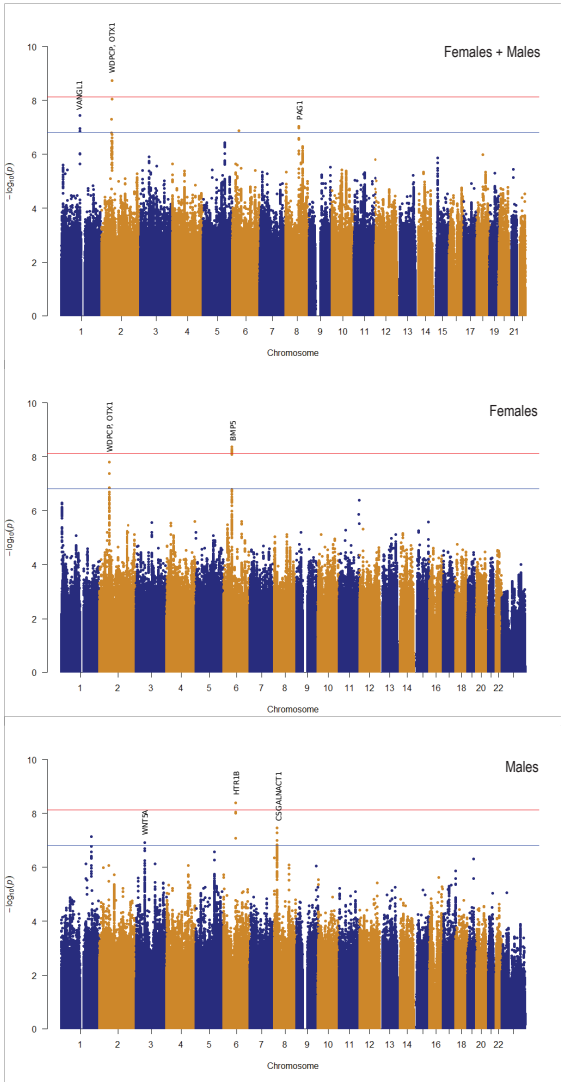
Size interval	CNVs in VUR (%)	CNVs in Controls (%)
100-500 kb	498 (76.5%)	8,130 (83.3%)
500-1,000 kb	84 (12.9%)	1,144 (11.72%)
1,000-2,000 kb	42 (6.45%)	379 (3.88%)
≥ 2,000 kb	27 (4.15%)	107 (1.1%)

Supplemental Table 2. VUR cases are enriched in large, rare CNVs, compared to controls. Counts (%) of rare (frequency in PCA-defined populations ≤ 0.1%), gene-intersecting CNVs within the indicated size intervals (kb). Fisher's Exact test $P = 1.98 \times 10^{-9}$.

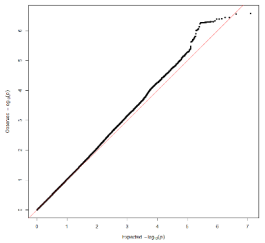


Supplemental Figure 3 VUR cases are enriched in larger rare CNVs as compared to controls. Proportion of CNVs within the indicated size intervals (kb). Inner rectangle encloses data shown in Figure 1B. Percentages are calculated in both figures based on the total number of rare, large (size ≥ 100 kb) CNVs (100%) for VUR cases and controls, respectively.

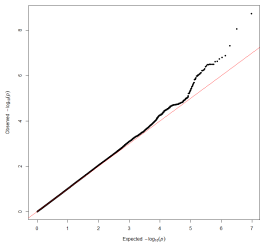
A



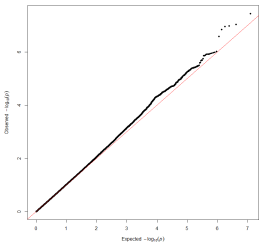
B



Additive model (λ=1.039)

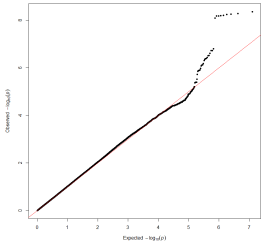


Recessive model (λ=1.023)

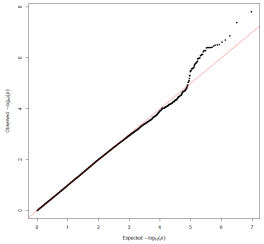


Dominant model (λ=1.034)

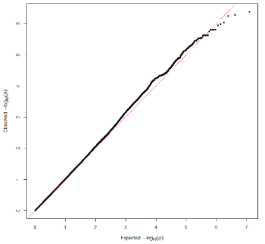
Females + Males



Additive model (λ=1.024)

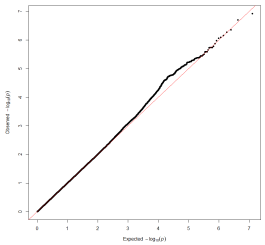


Recessive model (λ=0.99)

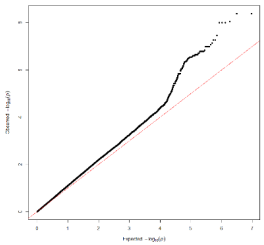


Dominant model (λ=1.025)

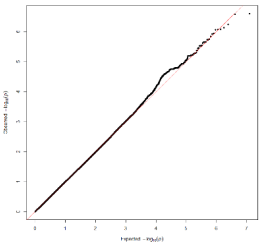
Females



Additive model (λ=1.009)



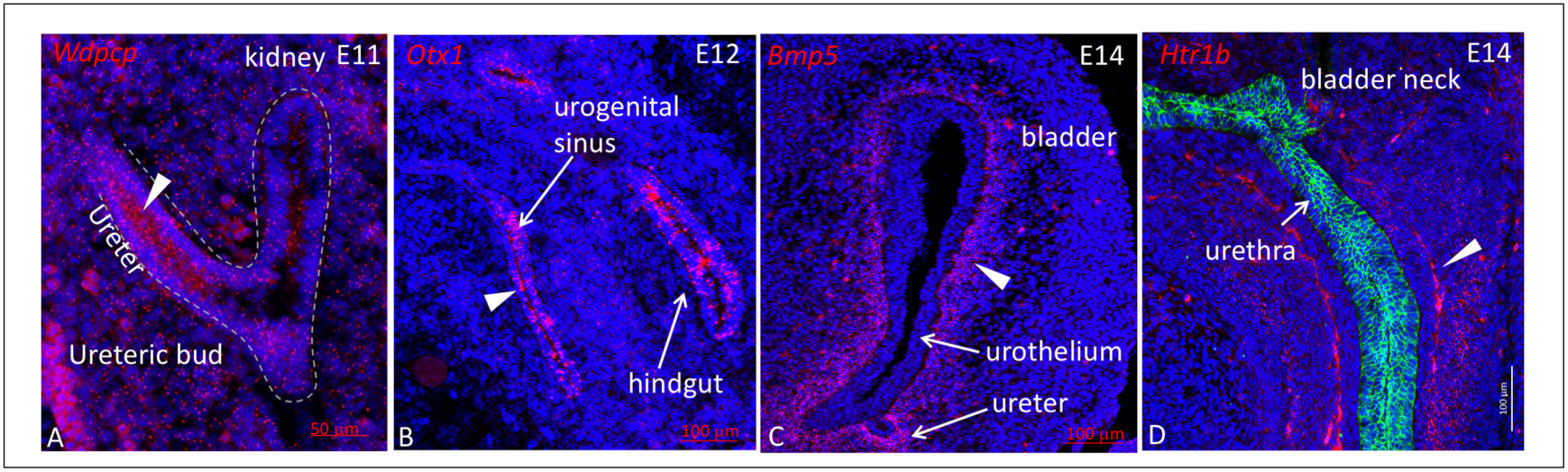
Recessive model (λ=1.13)



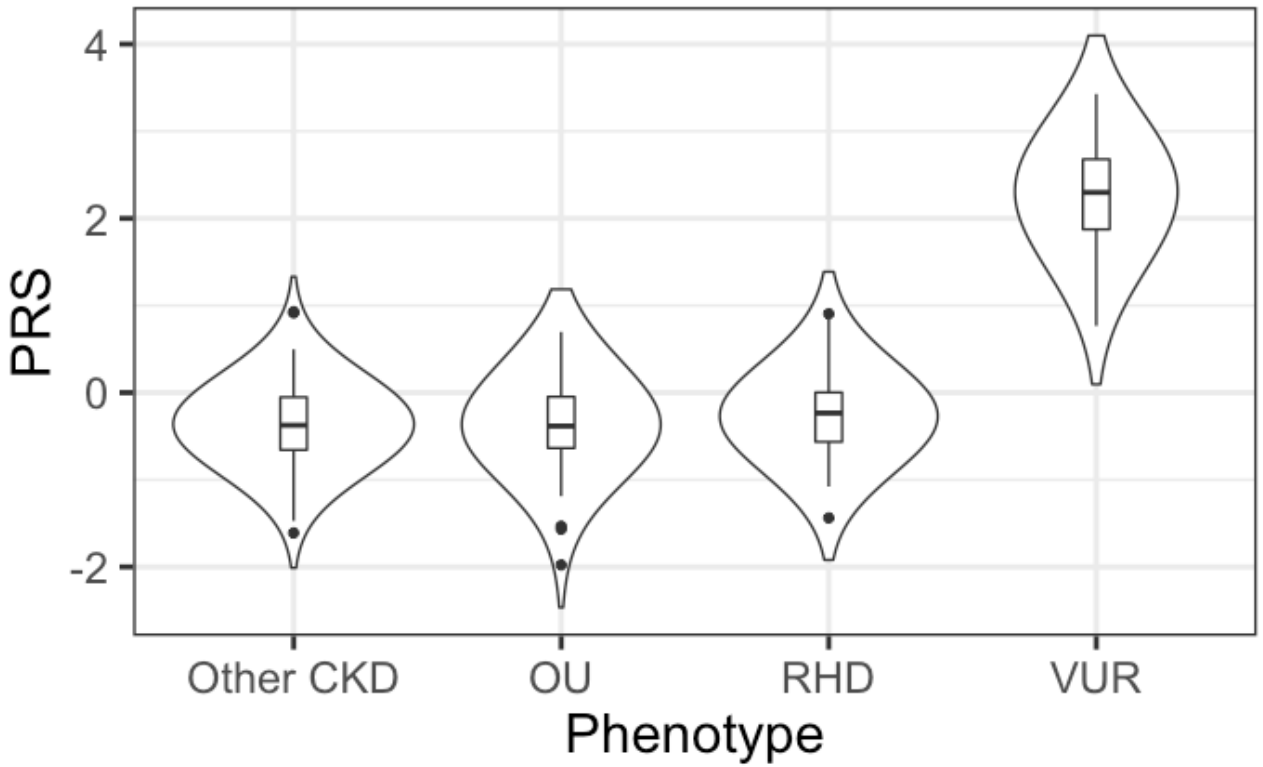
Dominant model (λ=0.99)

Males

Supplemental Figure 4. GWAS meta-analyses. (A) Manhattan plots of the combined GWAS under additive, recessive and dominant models, for both genders combined (top), females only (middle) and males only (bottom). The calculated -log10 P values are shown for each chromosome, according to genomic position (hg19). Text labels show symbols of genes at or near the top associated SNPs. **(B)** Q-Q plots for additive (left), recessive (center) and dominant (right) models in females and males combined (top), females (middle) and males (bottom). Estimated genomic inflation factors are shown.



Supplemental Figure 5. Expression of *Wdpcp*, *Otx1*, *Bmp5* and *Htr1b* in the mouse lower urinary tract. A. RNA-scope showing expression of *Wdpcp* in the ureteric bud trunk at E11 (white triangle). B. Expression of *Otx1* in the epithelium of the hindgut and urogenital sinus at E12 (white triangle points to the urogenital sinus). C. Expression of *Bmp5* in the sub-urothelial stroma at E14 (white triangle). D. Expression of *Htr1b* in endothelial cells adjacent to the urethral epithelium (white triangle).



Supplemental Figure 6. **Distribution of VUR PRS values across phenotypes in CKiD participants of European ancestry.**
Vesicoureteral reflux (VUR) cases were among the samples in the GWAS and therefore have larger PRS, as expected; shown only for reference. There were no significant differences ($P > 0.05$) between the other phenotypes compared. Other CKD: other chronic kidney disease; OU: obstructive uropathy; RHD: renal hypodysplasia.