Supplementary Information

Supplementary Methods

Primary MR implementation and reproducibility

Single-instrument traits were analyzed using the Wald ratio, while traits with at least two instruments were analyzed using multiplicative random-effects inverse-variance weighted MR (MRE-IVW). For MRE-IVW, the fixed-effect standard error was multiplied by $\sqrt{\max(1, Q/df)}$. This allowed residual heterogeneity to increase the standard error but prevented under dispersion from reducing it below the fixed-effect value. Primary MR estimates were taken from the prespecified result tables and were not replaced by default TwoSampleMR output.

MR assumptions and analytical safeguards

Interpretation of the primary MR estimates relied on the three-core instrumental-variable assumptions. Relevance was addressed by selecting cis-eQTL instruments at $P < 5 \times 10^{-8}$ and retaining only variants with $F > 10$. Independence was supported by stringent within-trait linkage-disequilibrium clumping at $r^2 < 0.001$ within 10 Mb and by restricting instruments to cis-regulatory variants, although independence from all unmeasured confounders cannot be verified from summary data. The exclusion-restriction assumption was examined, where instrument number permitted, using Cochran's Q, MR-Egger, weighted-median, MR-PRESSO, leave-one-out analyses, and regional colocalization. These analyses cannot exclude horizontal pleiotropy, particularly for traits represented by a single instrument. When these assumptions hold, the MR estimate can be interpreted as the effect of genetically proxied expression on CKD.

Colocalization inputs, outcome model and priors

The coloc.abf analysis used beta and varbeta for both datasets. For eQTLGen, the aligned effect estimate, standard error, allele-frequency input, and variant-specific sample size were supplied for a quantitative trait with `sdY` set to 1. For FinnGen, the effect estimate, standard error, alternate-allele frequency, total sample size of 492,013, and case fraction of 14,402/492,013 were supplied for a case-control outcome. The requested priors were $p_1 = p_2 = 1 \times 10^{-4}$ and $p_{12} = 1 \times 10^{-5}$. In dense regions, the effective values of p_1 and p_2 were capped at 0.99 divided by the number of matched variants. The effective value of p_{12} was additionally constrained so that it did not exceed either marginal prior.

Steiger directionality analysis

Exposure correlations were reconstructed with `TwoSampleMR::get_r_from_bsen` from the exposure effect estimate, standard error, and sample size. Equivalently, $F = (beta/SE)\text{^}2$ and $R^2 = F/(N - 2 + F)$. For binary CKD,

`TwoSampleMR::get_r_from_lor` used the outcome log-odds effect estimate, outcome allele frequency, 14,402 cases, 477,611 controls, `model = 'logit'`, `correction = FALSE`, and assumed population prevalences of 0.05, 0.10, and 0.15. SNP-specific R^2 values were summed across retained instruments and compared using `TwoSampleMR::mr_steiger`, which calls `psych::r.test`. This procedure provides a prevalence-informed latent-logit-scale approximation rather than a conventional liability- or probit-scale transformation. The resulting directionality findings are reported in Supplementary Table S7.

CKDGen identifier-harmonized sensitivity analysis

The 9,162,323-row CKDGen file was processed sequentially without loading the complete file into memory. The primary analysis retained only exact rsID matches. The identifier-harmonized sensitivity analysis additionally admitted requested variants that were uniquely concordant by chromosome, GRCh37 position, and both alleles. No linkage-disequilibrium proxy, nearest variant, or substitute biological variant was used. Exact-rsID matches reproduced the primary estimates to numerical precision, and recovered aliases were analyzed using the same Wald-ratio or MRE-IVW procedures.

Renal standardized effects and random-effects synthesis

Renal expression and renal meta-analysis were treated as separate evidence domains. GSE66494 provided the prespecified primary single-cohort contrast, while GSE104954 provided an independent measured contrast. Direction-concordant evidence with FDR < 0.05 was required for independent renal support. For each eligible contrast, the approximate standardized mean difference was calculated as $d = t_{mod}\sqrt{(1/n_{case} + 1/n_{control})}$, where $t_{mod} = effect/SE$ was the limma moderated statistic. Hedges' g was then calculated as $g = J \times d$, where $J = 1 - 3/(4df - 1)$ and $df = n_{case} + n_{control} - 2$. Sampling variance was estimated using the prespecified large-sample approximation $Var(g) = (n_{case} + n_{control})/(n_{case}\, n_{control}) + g^2/(2df)$. Within each disease and compartment stratum, at least two independent groups were required for random-effects synthesis with `metafor::rma.uni(yi = hedges_g, vi = var_hedges_g, method = 'REML', test = 'z')`. Representative strata were selected according to cohort count, total sample size, and pooled standard error without reference to P values or FDR. Domain-level renal states were based on all prespecified strata and could therefore be classified as mixed.

Evidence-domain decision rules

The eight evidence domains were evaluated without assigning a composite score. MR support was defined as FDR < 0.05, while Bonferroni support required $P < 3.27 \times 10^{-6}$. Colocalization support required PP.H4 ≥ 0.50, with moderate and strong categories retained separately in the source table. Independent CKD evidence was classified as supported when an estimate was available, direction-concordant with FinnGen, and nominally significant at P < 0.05. An available direction-concordant estimate with P ≥ 0.05 was classified as no support detected, while an opposite-direction estimate was classified as direction-discordant. Renal-expression support required an

FDR-significant prespecified primary contrast or an FDR-significant direction-concordant independent contrast. Renal-meta support required a direction-concordant pooled estimate with global FDR < 0.05 within an eligible stratum. A significant opposite-direction stratum was classified as direction-discordant, while loci without an eligible stratum were classified as unavailable. Kidney eQTL evidence was supported by an eGene result or a direction-concordant allele-resolved overlap with a significant eQTL pair. Evidence was classified as direction-discordant when only discordant overlaps were observed. Single-nucleus localization was considered detected when at least one annotated cell type included at least three donors and showed donor-balanced non-zero expression of at least 5%.

Software and computational implementation

Analyses were conducted in R 4.6.1. Steiger analyses used `TwoSampleMR 0.6.29` and `psych 2.6.5`. Renal random-effects models used `metafor 5.0-1`. Colocalization was implemented with `coloc.abf`, and multi-signal colocalization was attempted with SuSiE only when the prespecified local linkage-disequilibrium coverage criterion was met. Analysis-specific settings are reported in the corresponding sections above.

Large-file processing and reproducibility

Large eQTLGen and CKDGen inputs were processed using streaming, chunked workflows, or disk-backed intermediate files. The complete input files were not loaded into memory. Failed runs terminated with visible errors and were rerun from the beginning after the underlying issue had been corrected.

Supplementary figure legends

Supplementary Figure S1. Instrument-count distribution. The number of retained instruments is shown for all 28 FDR-significant expression traits.

Supplementary Figure S2. MR scatter plots and MR-method comparisons. SNP-expression and SNP-CKD effects and side-by-side method estimates are shown for the five traits with at least three retained instruments. The primary line and estimate correspond to MRE-IVW. Weighted-median and MR-Egger estimates are displayed only where applicable and do not replace the primary estimate.

Supplementary Figure S3. Leave-one-out analyses. Primary and single-omission estimates are shown for the five eligible traits. TUBB contains the only omission that met the prespecified influence rule. No omission reversed the direction of effect.

Supplementary Figure S4. Funnel plots. SNP-specific Wald estimates are plotted against precision for the five eligible multi-instrument traits. RP11-137H2.4 and TUBB each have only three instruments and are marked as having limited interpretability. Funnel symmetry was not inferred for these traits.

Supplementary Figure S5. MR sensitivity matrix. Applicability and results of Cochran Q, MR-Egger, weighted median, MR-PRESSO, Steiger directionality and leave-one-out analyses are shown for all 28 FDR-significant traits.

Supplementary Figure S6. SNP-level MR forest plots. SNP-specific Wald log-odds estimates and 95% confidence intervals are shown for C4A, IER3, PSORS1C3, RP11-137H2.4, and TUBB. Dashed lines indicate the corresponding primary MRE-IVW estimate. SNP-specific estimates are shown for diagnostic purposes and do not replace the primary results.

Supplementary Figure S7. MHC-excluded MR sensitivity overview. The nine non-MHC FDR-significant expression traits map to eight loci. Two traits meet the Bonferroni threshold and two show strong colocalization. Primary MR estimates are unchanged.

Supplementary Figure S8. Complex MHC locus. Genomic positions, MR estimates, FDR strength and colocalization categories are shown for all 19 MHC expression traits. The display retains trait-level transparency without implying independent gene discoveries.

Supplementary Figure S9. C4A regional colocalization. Regional eQTL and CKD association signals are shown across the C4A locus under the single-signal colocalization model.

Supplementary Figure S10. C4B regional colocalization. Regional eQTL and CKD association signals are shown across the C4B locus under the single-signal colocalization model.

Supplementary Figure S11. CYP21A2 regional colocalization. Regional eQTL and CKD association signals are shown across the CYP21A2 locus under the single-signal colocalization model.

Supplementary Figure S12. KIAA1919 regional colocalization. Regional eQTL and CKD association signals are shown across the KIAA1919 locus under the single-signal colocalization model.

Supplementary Figure S13. TNXA regional colocalization. Regional eQTL and CKD association signals are shown across the TNXA locus under the single-signal colocalization model.

Supplementary Figure S14. Colocalization summary. Posterior support and prespecified colocalization categories are summarized for all 28 FDR-significant expression traits.

Supplementary Figure S15. Locus-definition sensitivity. The number of connected components is compared across physical-distance and lead-eQTL linkage-disequilibrium thresholds and a shared-instrument/LD-only definition.

Supplementary Figure S16. Evidence-score sensitivity. Descriptive, equal-domain, genetic-heavy, missingness-aware, and leave-one-domain-out scores are retained only as sensitivity analyses. They do not determine the ordering of candidates in the main analysis.

Supplementary Figure S17. Kidney eQTL evidence. Kidney-specific eQTL support is shown for FDR-significant expression traits with available evidence.

Supplementary Figure S18. Normal-kidney single-nucleus expression. Expression localization of FDR-significant expression traits is shown across annotated kidney cell types where gene mapping and expression data were available.

Supplementary Figure S19. Renal multicohort meta-analysis. Standardized renal expression contrasts, pooled estimates and heterogeneity are shown across the included renal cohorts and eligible traits.

Supplementary Figure S20. CKDGen exact-rsID and identifier-harmonized comparison. Primary exact-rsID estimates are shown alongside secondary estimates obtained after unique coordinate-and-allele alias recovery. The secondary analysis recovered 27 unique aliases without linkage-disequilibrium proxies, made all 28 traits estimable, and identified four FDR-significant direction-concordant traits within the complex MHC locus. This sensitivity analysis does not replace the primary exact-rsID analysis and does not resolve gene attribution within L03.

Supplementary Figure S21. Instrument-count-stratified Q-Q diagnostic. Observed and expected -log10 P values are shown for all 15,285 expression traits and separately for traits with one, two, and at least three retained instruments. These panels provide global diagnostics for the analyzed trait sets. Differences between strata should not be interpreted as independent genomic inflation estimates because expression traits and instruments are correlated.

Supplementary Figure S22. CLNS1A regional colocalization. All matched regional variants are shown in separate cis-eQTL and CKD association tracks with lead-variant rsIDs, gene annotations, PP.H4, matched-variant count and local minimum P values. The panel is supplementary because the main regional figure is restricted to the three strong-colocalization traits.

Supplementary table legends

Supplementary Table S1. Data resources and provenance. Dataset versions, access locations, checksums and analysis roles.

Supplementary Table S2. Complete primary MR results. Primary results for all 15,285 tested expression traits.

Supplementary Table S3. FDR-significant expression traits. Primary estimates, FDR values, locus assignments, and colocalization annotations for all 28 FDR-significant traits.

Supplementary Table S4. Instrument-level MR data. Harmonized instrument records underlying the primary screen.

Supplementary Table S5. Instrument-strength statistics. SNP-level and trait-level F statistics.

Supplementary Table S6. Harmonization audit. Allele alignment, exclusions and retained records.

Supplementary Table S7. MR sensitivity matrix. Applicability and results of heterogeneity, MR-Egger, weighted median, MR-PRESSO, Steiger and leave-one-out analyses.

Supplementary Table S8. Leave-one-out results. Primary and single-omission estimates for eligible traits.

Supplementary Table S9. MHC-exclusion sensitivity. Discovery counts with and without the reference MHC interval.

Supplementary Table S10a. Gene-to-locus map. Mapping of the 28 candidates to nine connected loci.

Supplementary Table S10b. Expression-trait identifier and gene-symbol map. Ensembl v71 identifiers and display symbols for all tested expression traits.

Supplementary Table S11. Locus-definition sensitivity. Connected-component counts and membership under alternative distance and LD rules.

Supplementary Table S12. Colocalization results. Regional inputs, posterior probabilities and prespecified evidence categories.

Supplementary Table S13. Colocalization-prior sensitivity. Results across prespecified shared-variant priors.

Supplementary Table S14. SuSiE attempts. LD coverage, convergence and explicit unavailable states.

Supplementary Table S15a. Requested CKDGen instruments. Instrument identifiers and requested alleles for independent-outcome analysis.

Supplementary Table S15b. CKDGen exact-rsID matching. Primary exact-rsID matching states and unavailable variants.

Supplementary Table S16. Primary exact-rsID CKDGen analysis. Trait-level estimates, direction concordance, and replication-wide FDR.

Supplementary Table S17. Renal GEO datasets. Included Series, original publication, PMID, DOI, disease, compartment, platform and sample-size metadata.

Supplementary Table S18. Renal expression contrasts. Eligible standardized contrasts and independence selection.

Supplementary Table S19. Renal random-effects meta-analysis. Pooled Hedges g estimates, uncertainty, heterogeneity and global FDR.

Supplementary Table S20. Kidney eQTL evidence. eGene and allele-resolved instrument-overlap evidence from GTEx and the Kidney eQTL Atlas.

Supplementary Table S21. Normal-kidney single-nucleus expression. Donor- and cell-type-level descriptive localization.

Supplementary Table S22. Locus evidence landscape. Prespecified genetic and contextual evidence states are reported without a composite ranking. Table notes define the decision rule and threshold for each of the eight evidence domains.

Supplementary Table S23. Evidence-weight sensitivity. Alternative descriptive scores retained only as sensitivity analyses.

Supplementary Table S24. CKDGen identifier recovery. Exact matches, unique coordinate-and-allele aliases, and the single unavailable request are reported. No linkage-disequilibrium proxy was used.

Supplementary Table S25. Identifier-harmonized CKDGen sensitivity. Secondary trait-level estimates, direction concordance, nominal significance and analysis-specific FDR.