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Understanding cell-type convergence of kidney disease and traits through interpretable eQTLs informed by single-cell epigenomic data

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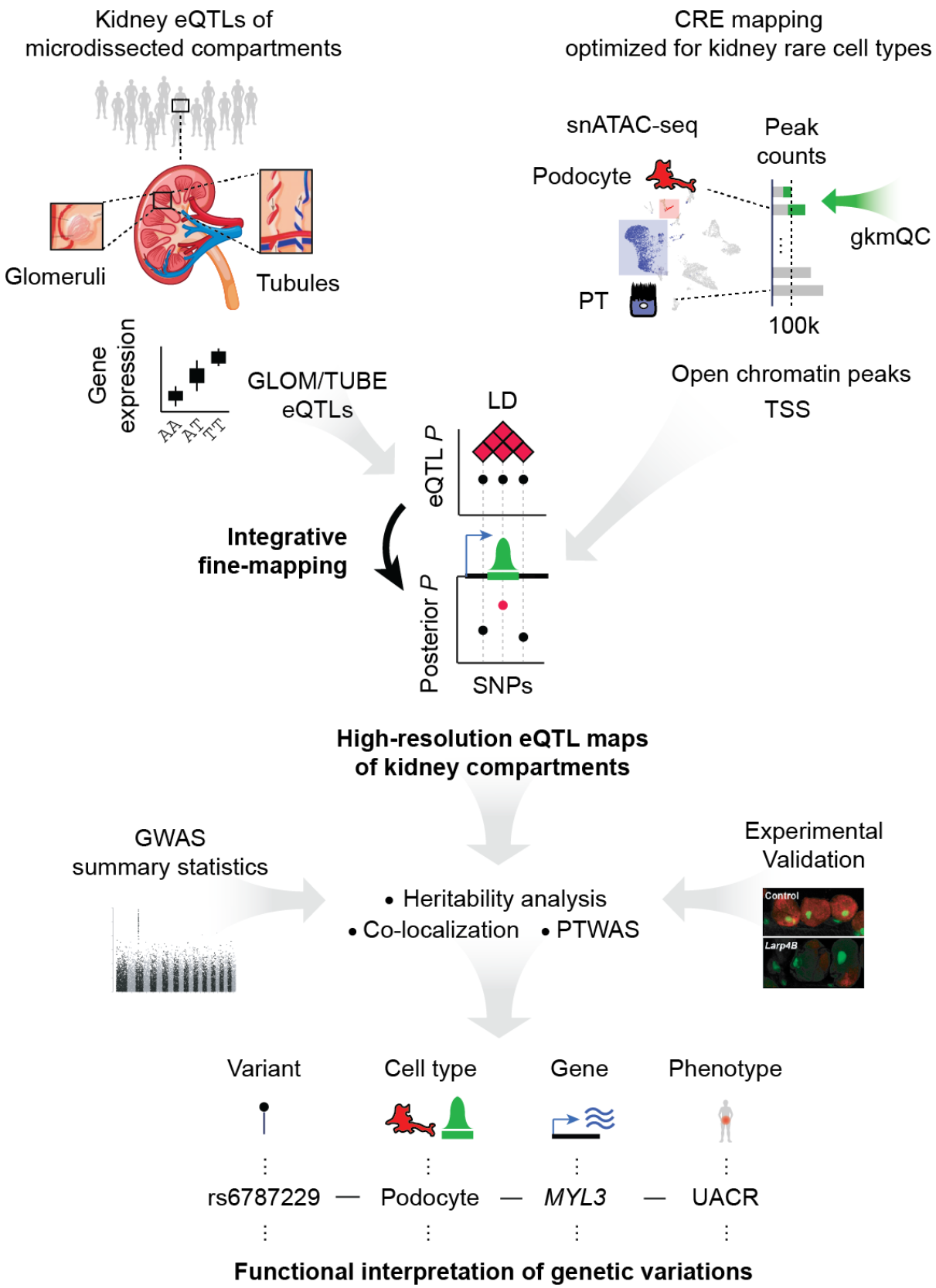
Objectives: Genomic contributors to kidney traits extend beyond rare, pathogenic, exonic variants. Genome-wide association studies (GWAS) have demonstrated that heritability of diverse kidney traits are polygenic and primarily non-coding. Expression quantitative trait locus (eQTL) studies illuminate genomic variants that regulate specific genes providing biological insight and fine mapping of GWAS loci. Single-cell epigenomic data can aid fine-mapping of eQTLs to identify kidney regulatory variants from tag-SNPs within same haplotype block.

Methods: Using 240 glomerular (GLOM) and 311 tubulointerstitial (TUBE) micro-dissected samples from human kidney biopsies, we discovered 5,371 GLOM and 9,787 TUBE genes with at least one variant significantly associated with expression (eGene) by incorporating kidney single-nucleus open chromatin data and transcription start site distance as an "integrative prior" for Bayesian statistical fine-mapping.

Results: The use of an integrative prior resulted in higher resolution eQTLs illustrated by (1) smaller numbers of variants in credible sets with greater confidence, (2) increased enrichment of partitioned heritability for GWAS of two kidney traits, (3) an increased number of variants colocalized with the GWAS loci, and (4) enrichment of computationally predicted functional regulatory variants. A subset of variants and genes were validated experimentally *in vitro* and using a *Drosophila* nephrocyte model.

Conclusions: The eQTLs augmented by cell-type CREs make the results of downstream analyses interpretable in terms of (1) mechanistic insight into transcriptional regulation and (2) contributing cell-types or *cis*-regulatory elements. Interactive visualizations of eQTLs provided in www.nephqtl2.org will be a novel resource to narrow down potential mechanisms and elucidate the regulatory landscape of kidney phenotypes.

Figure 1. Analysis schematic: Integrating eQTLs with cell-type cis-regulatory annotations to build high-resolution eQTL maps of micro-dissected glomeruli (GLOM) and tubulointertisium (TUBE)


Kidney eQTLs of
microdissected compartments
Glomeruli
Tubules
Gene expression
AA
AT
TT
GLOM/TUBE
eQTLs
CRE mapping
optimized for kidney rare cell types
snATAC-seq
Peak
counts
Podocyte
gkmQC
PT
100k
Open chromatin peaks
TSS
LD
eQTL P
Integrative
fine-mapping
Posterior P
SNPs
High-resolution eQTL maps
of kidney compartments
GWAS
summary statistics
• Heritability analysis
• Co-localization • PTWAS
Experimental
Validation
Control
Larp4B
Variant
Cell type
Gene
Phenotype
rs6787229 — Podocyte — MYL3 — UACR
Functional interpretation of genetic variations