A catalogue of molecular targets for kidney function from genetic analyses of a million individuals

Supplementary Materials

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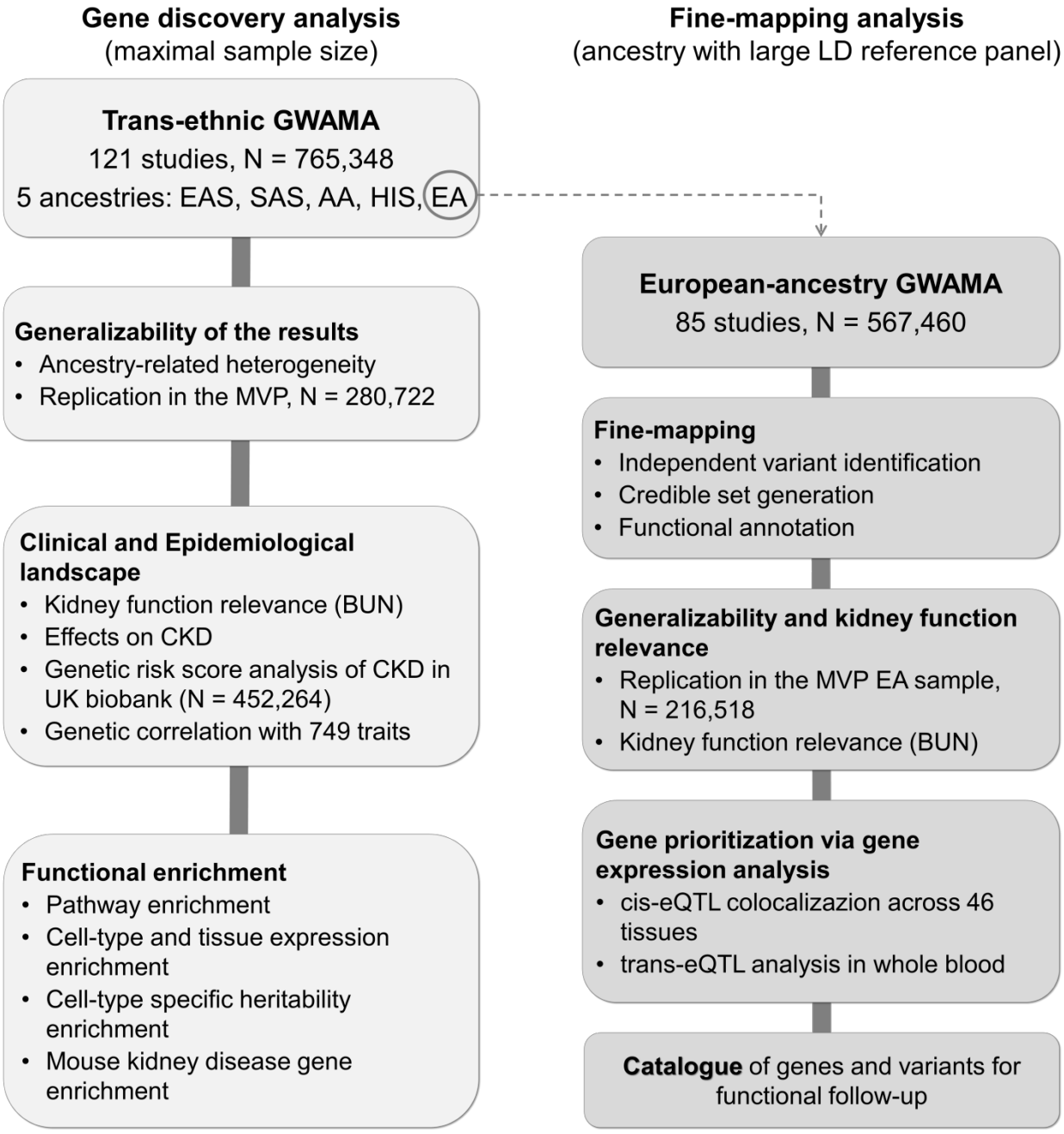
Supplementary Tables are provided separately as a spreadsheet.

Supplementary Figure 1: Analysis Flowchart

Panel A. Flowchart of trans-ethnic GWAS meta-analysis (GWAMA) and follow-up to discover and characterize genetic associations with kidney function. **Panel B.** Fine-mapping and co-localization analyses to highlight effector genes and causal variants among participants of EA.



Supplementary Figure 2: Regional Association Plots

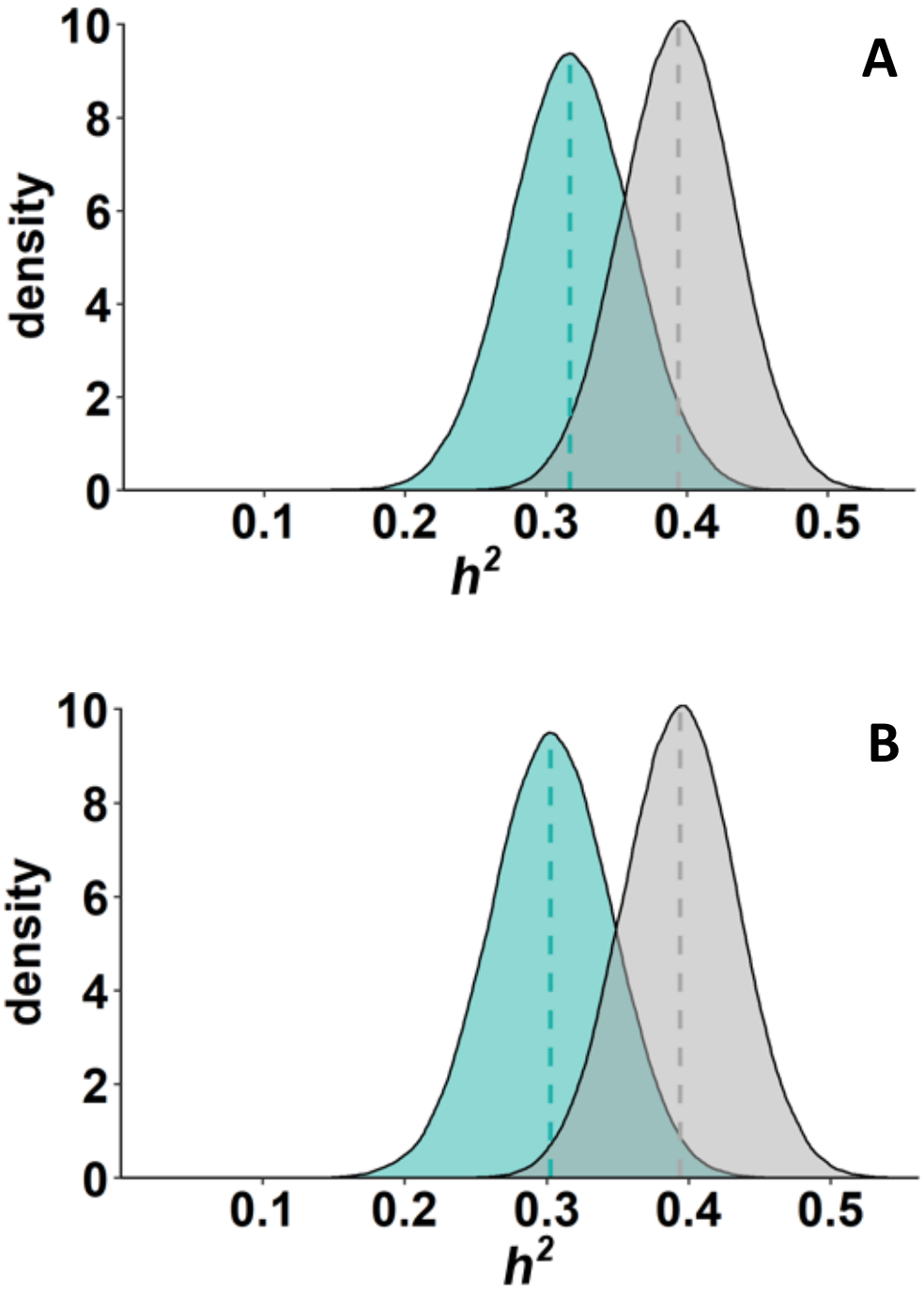
Regional Association Plot Booklet for all 308 loci identified in association with eGFR through trans-ethnic meta-analyses.

PDF-booklet available online:

https://www.dropbox.com/s/snf5xyqgpi0sbll/RAPs_ALL_4_per_page.pdf?dl=0

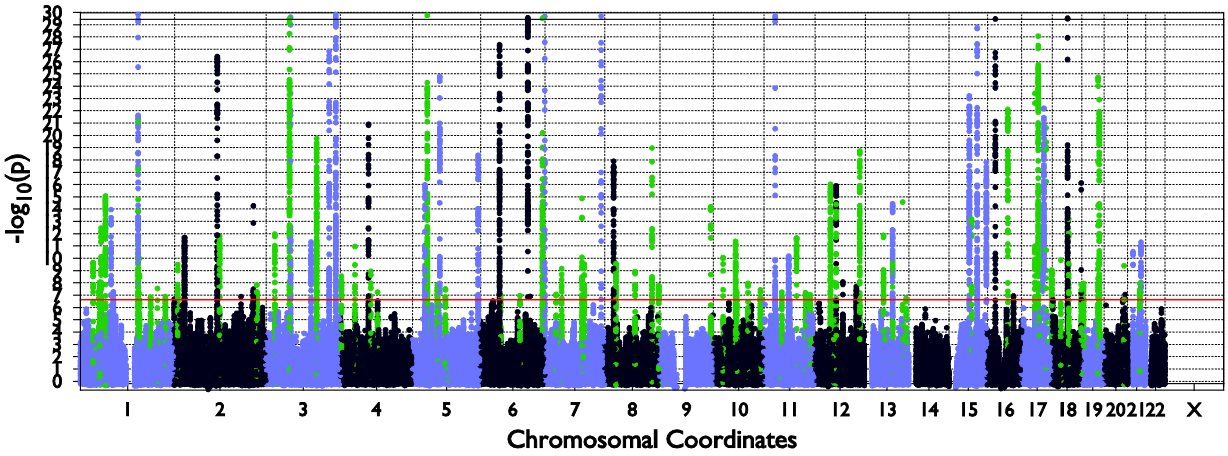
Supplementary Figure 3: Genetic Heritability

Distribution of the genetic heritability (h^2) estimates of age- and sex-adjusted log(eGFR) residuals in the Cooperative Health Research In South Tyrol (CHRIS) study, for index SNPs from the trans-ethnic (**Panel A**) and EA-specific (**Panel B**) GWAS. h^2 distribution is shown before (gray) and after (green) inclusion of the index SNPs into the model, with the shift representing the amount of h^2 explained by the index SNPs.



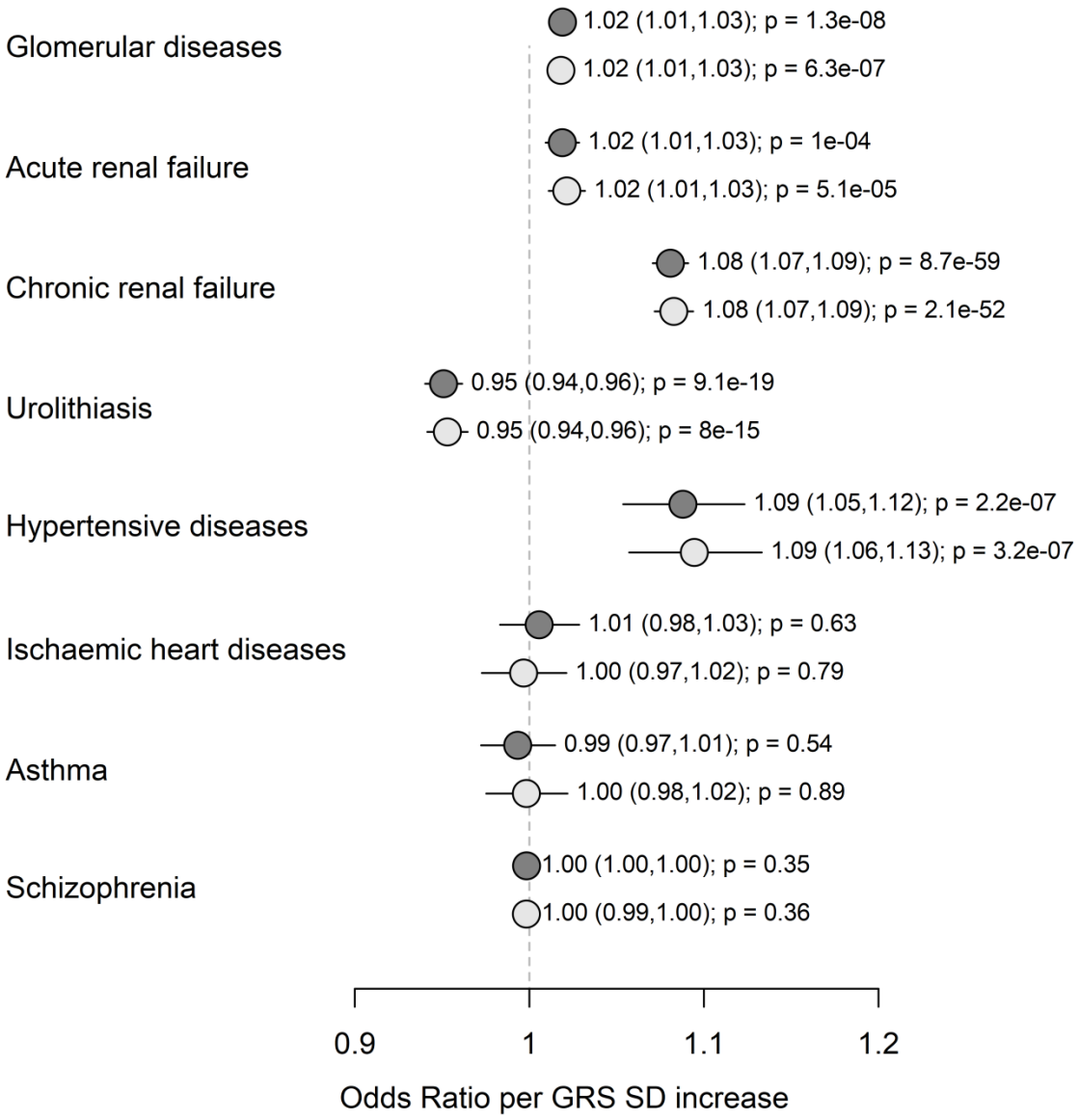
Supplementary Figure 4: BUN Manhattan plot

Manhattan plot of results from the GWAS meta-analysis of blood urea nitrogen (BUN).



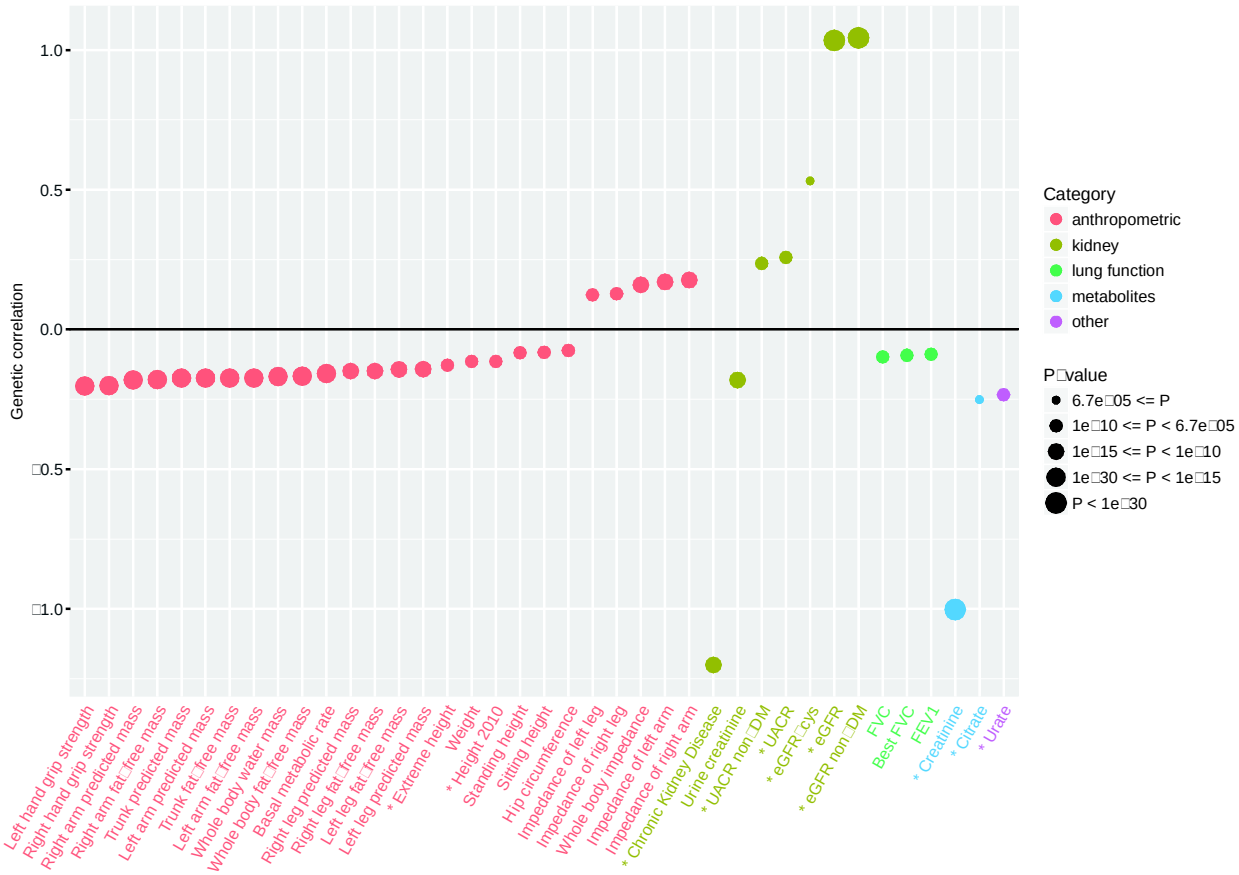
Supplementary Figure 5: Genetic Risk Score

Association between a genetic risk score (GRS) for low eGFR and clinical phenotypes abstracted from ICD-10 codes independent individuals from the UK Biobank. Asthma and Schizophrenia were included as a negative control. Displayed are odds ratios and their 95% CIs per standard deviation increase in GRS (Methods).



Supplementary Figure 6: Genetic correlation plot

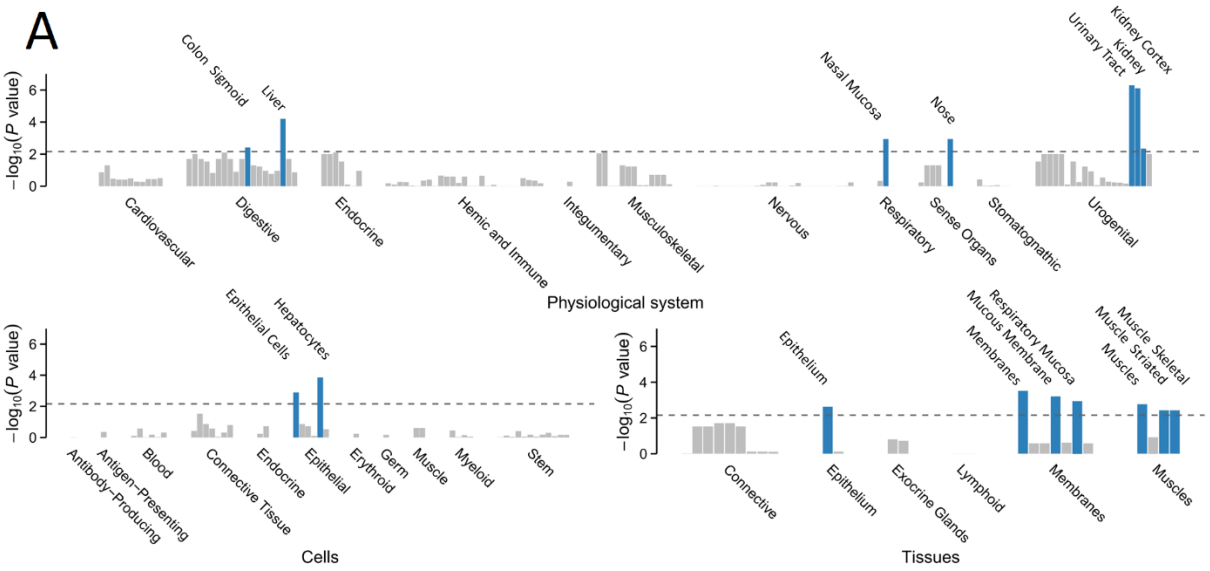
Genetic correlation plot based on the summary statistics from the trans-ethnic GWAS meta-analysis of eGFR and 748 other complex traits and diseases available through LD Hub.



The genetic correlations with citrate and cystatin C were not significant (P=6.0×10^{-4} and 4.0×10^{-4}, respectively, **Supplementary Table 8**), because these traits were measured in a limited number of studies, resulting in smaller GWAS sample sizes.

Supplementary Figure 7: Pathway and tissue enrichment analysis with DEPICT

Shown is the barplot of the results of the tissue and cell type enrichment analysis in **Panel A**. Cells, tissues and physiological systems are highlighted in blue, if the association FDR was smaller than 0.05 and are summarized in the table in **Panel B**. **Panel C** illustrate the highly correlated and strongly associated meta gene sets (P <1.x10^{-6}, FDR <0.05) from the pathway and gene-set enrichment analysis clustered according to their biological relevance for kidney function, energy metabolism and signaling and transcription.



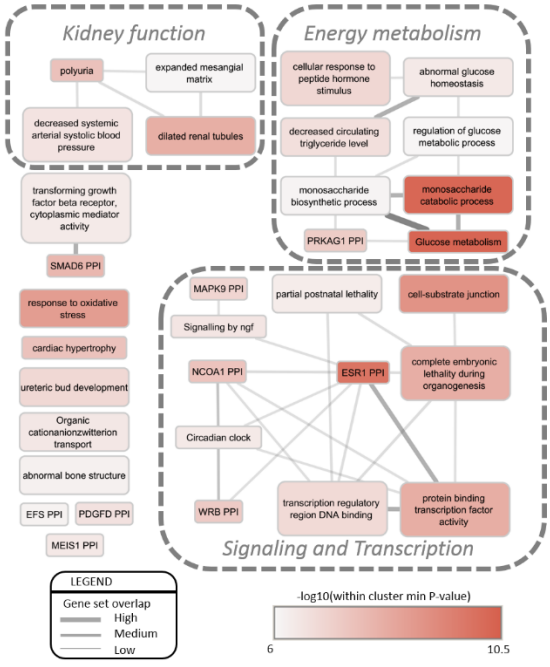
B

Enriched tissues and cell types identified by DEPICT. Shown are the tissues and cell types significantly (FDR<0.05) enriched in the meta-analysis results of subjects from all ethnicities.

MeSH term	Name	MeSH 1st level term	MeSH 2nd level term	Nominal P-value
A05.810	Urinary Tract	Urogenital System	Urinary Tract	4.99x10^{-7}*
A05.810.453	Kidney	Urogenital System	Urinary Tract	7.84x10^{-7}*
A03.620	Liver	Digestive System	Liver	6.46x10^{-5}*
A11.436.348	Hepatocytes	Cells	Epithelial Cells	1.38x10^{-4}*
A10.615	Membranes	Tissues	Membranes	3.14x10^{-4}*
A10.615.550	Mucous Membrane	Tissues	Membranes	6.30x10^{-4}*
A10.615.550.760	Respiratory Mucosa	Tissues	Membranes	1.15x10^{-3}
A04.531.520	Nasal Mucosa	Respiratory System	Nose	1.15x10^{-3}
A09.531	Nose	Sense Organs	Nose	1.15x10^{-3}
A11.436	Epithelial Cells	Cells	Epithelial Cells	1.28x10^{-3}
A10.690	Muscles	Tissues	Muscles	1.72x10^{-3}
A10.272	Epithelium	Tissues	Epithelium	2.42x10^{-3}
A10.690.552	Muscle Striated	Tissues	Muscles	3.78x10^{-3}
A10.690.552.500	Muscle Skeletal	Tissues	Muscles	3.78x10^{-3}
A03.556.249.249.356.668	Colon Sigmoid	Digestive System	Gastrointestinal Tract	3.90x10^{-3}
A05.810.453.324	Kidney Cortex	Urogenital System	Urinary Tract	4.64x10^{-3}

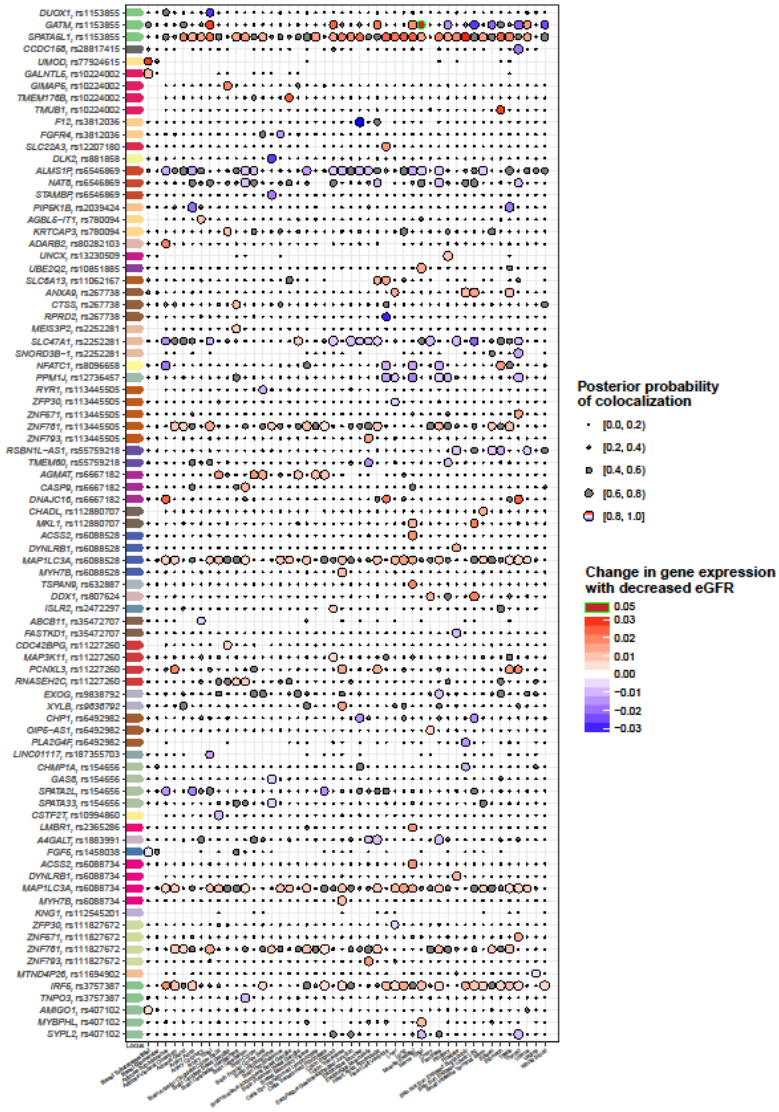
MeSH = Medical Subject Heading, MeSH 1st level term is given as Cells, Tissues or as the respective annotation in the Physiological system, Nominal P-values with * indicate a False Discovery Rate < 0.01

C

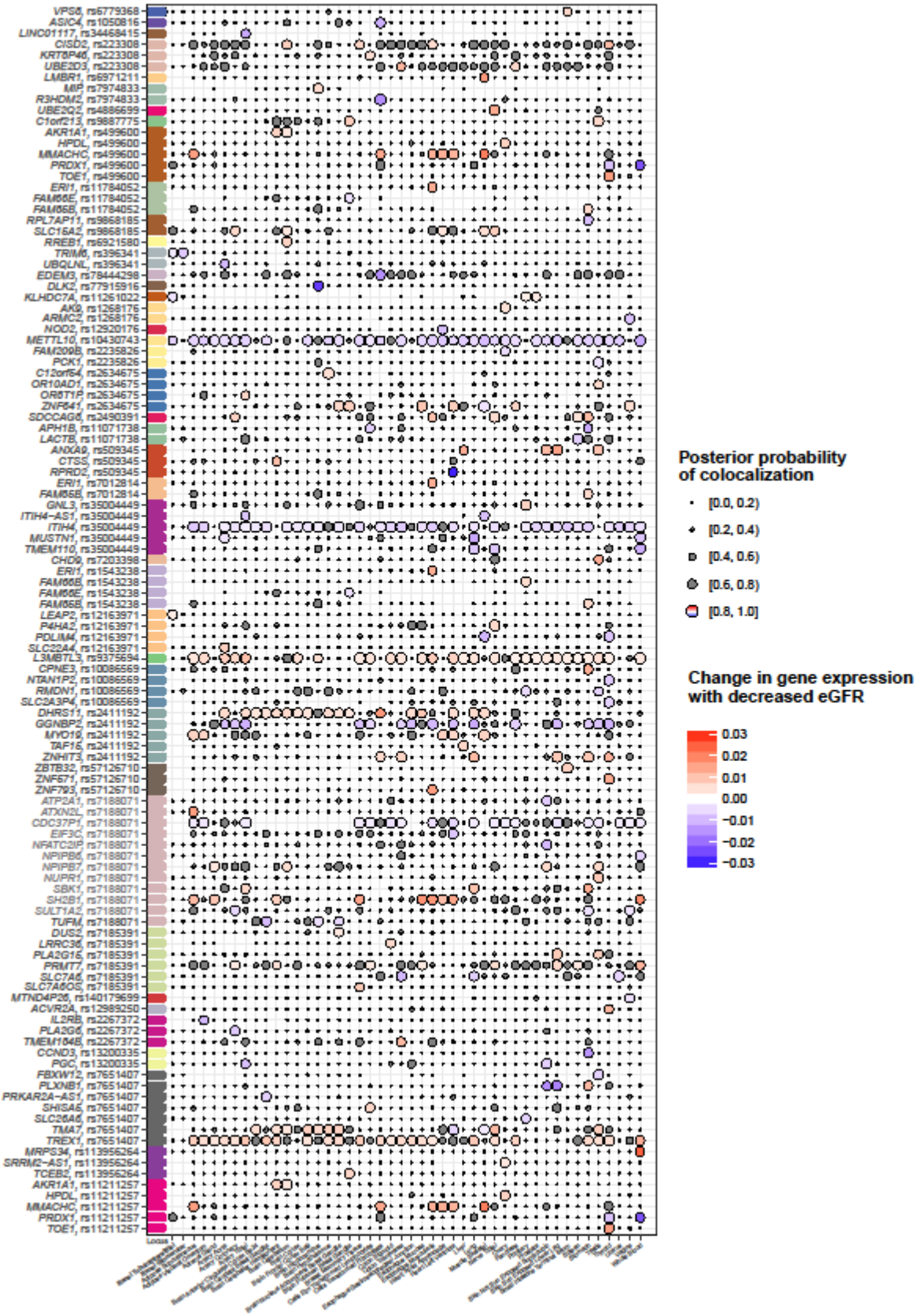


Supplementary Figure 8: Co-localization of eGFR-association signals with gene expression across 44 GTEx tissues and two kidney tissues

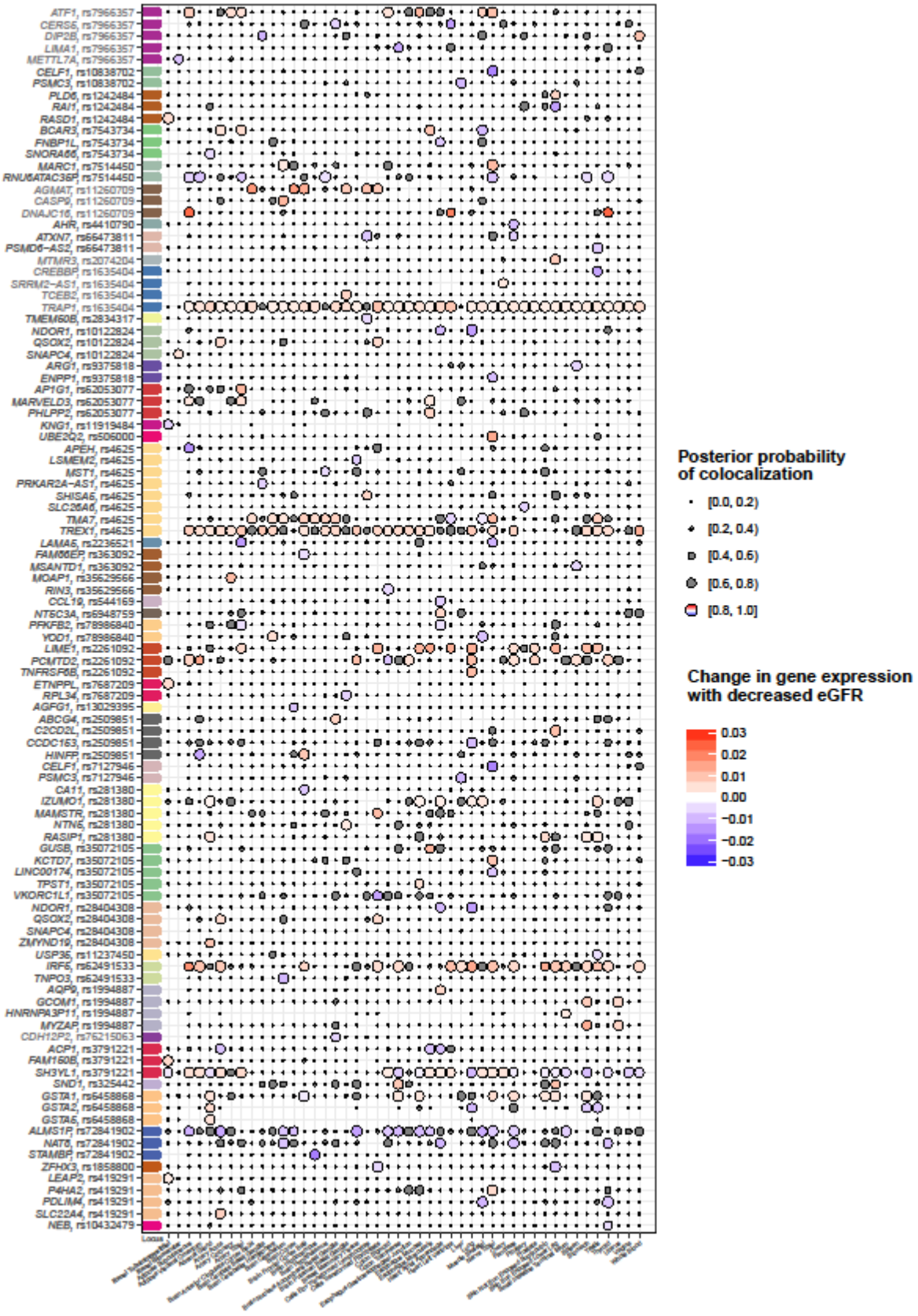
All eGFR loci were tested for co-localization with all eQTLs where the eQTL cis-window overlapped (±100 kb) the sentinel genetic variants. Genes with at least one positive co-localization (posterior probability of one common causal variant, H4, ≥0.80) in any of the 44 tissues for which eQTL data was released by the GTEx Project or in two renal tissue are illustrated with the respective sentinel variants (Y-axis). Co-localizations across all tissues (X-axis) are illustrated as dots, where the size of the dots indicates the posterior probability of the co-localization. Negative co-localizations (posterior probability of H4 <0.80) are grey, while the positive co-localizations are color-coded based on the predicted change in expression relative to the allele associated with lower eGFR.



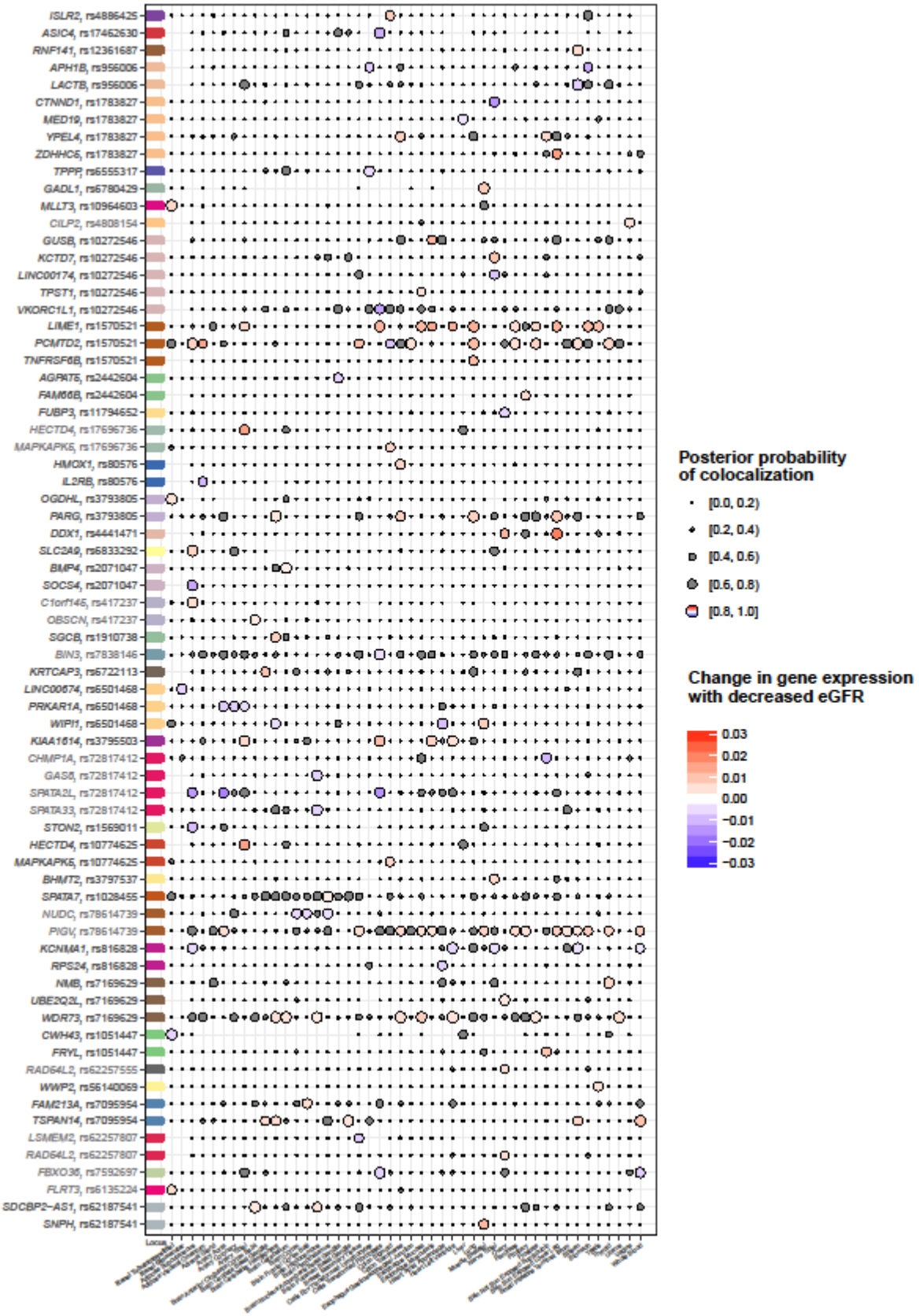
Supplementary Figure 8 – continued (2/4)



Supplementary Figure 8 – continued (3/4)



Supplementary Figure 8 – continued (4/4)



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