Target genes, variants, tissues and transcriptional pathways influencing human serum urate levels

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SUPPLEMENTARY INFORMATION

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Supplementary Note

Ancestry-specific meta-analyses of serum urate

In addition to the trans-ethnic meta-analysis, ancestry-specific GWAS meta-analyses were also conducted. Genome-wide significant loci for each ancestry group are summarized in **Supplementary Tables 5-8**. Five of 123 EA-specific significant loci were ancestry-specific, i.e. not contained within the 183 significant trans-ethnic loci (**Supplementary Table 5**). Among 14 significant loci in AA, five were ancestry-specific (**Supplementary Table 6**), and among the 46 significant loci in EAS, seven were ancestry-specific (**Supplementary Table 7**). None of the six genome-wide significant loci in SA was ancestry-specific (**Supplementary Table 8**). The ancestry-specific findings contained several plausible candidates, including *NIPAL1* in EA, a risk locus previously identified for renal under-excretion gout[1], and rs334 at *HBB* in AA, encoding the sickle cell allele. This finding is consistent with higher urate levels and gout incidence in sickle cell disease patients as compared to the general population[2].

Association between urate-associated SNPs and gene expression in *trans*

We investigated whether any trans-ethnic index SNPs or their proxies were reproducibly associated with gene expression in *trans* in whole blood or peripheral blood mononuclear cell in large eQTL studies (Methods). A total of 17 inter-chromosomal trans-eQTLs based on five index SNPs were identified (**Supplementary Table 21**). The urate-increasing allele of the index SNP rs174594 at *FADS2* on chromosome 11 was associated with higher expression of *LDLR* on chromosome 19 in two independent studies. Higher *LDLR* expression under inflammatory conditions was reported to promote transformation of macrophages into foam cells leading to increased vascular calcification.[3] The urate-increasing allele of the intronic SNP rs12530084 in *RREB1* on chromosome 6 was associated with higher expression of *SYT11* on chromosome 1 in two independent studies. *SYT11* is involved in calcium-dependent regulation of membrane trafficking in synaptic transmission, and both *RREB1* and *SYT11* are predominantly expressed in brain cerebellum. In addition, *SYT11* maps into one of the novel urate-associated loci identified in this study. The associated trans-eQTLs were enriched for several pathways as summarized in the GO, KEGG and Reactome databases (**Supplementary Table 22**), as well as for “cardiovascular disease” based on the Human Disease Ontology database.[4]

Phenotype generation and quality control of study-specific results

We developed an automated analysis workflow to collect and integrate results from 74 GWAS of serum urate from five ancestry groups participating in the CKDGen Consortium. We used a distributive model for study-specific GWAS, with meta-analyses conducted centrally. An analysis plan was circulated to all participating studies accompanied by custom shell and R scripts for phenotype generation (https://github.com/genepi-freiburg/ckdgen-pheno). Study-specific GWAS were conducted after centralized review and approval of the phenotype summary statistics.

Genotype imputation was conducted by each study. Haplotypes were estimated using MACH[5], ShapeIT[6], Eagle[7], or Beagle[8]. Imputation of genotypes was conducted using reference panels from the Haplotype Reference Consortium (HRC) version 1.1[9], 1000 Genomes Project (1000G) phase 3 v5 ALL, or the 1000G phase 1 v3 ALL[10] and ImputeV2[11], minimac3[12], PBWT[13], the Sanger[14], or the Michigan Imputation Server[12]. The imputed genetic dosages were annotated using NCBI b37 (hg19). Each study provided an imputation quality for each variant: ImputeV2 info score, the MACH/minimac RSQ or the SNPTest info score.

Study-specific GWAS results were checked using GWAtoolbox[15], including *P*-value inflation, allele frequency distribution, imputation quality, and completeness of genotypes. Custom scripts were used to compare imputed allele frequencies to those of ancestry-matched reference panels and to visualize variant positions. In addition, quality metrics, including the genomic control factor[16], were compared across studies.

DEPICT analysis details for functional enrichment

DEPICT performs gene set enrichment analysis by testing whether genes in 14,461 reconstituted gene sets were enriched for urate-associated SNPs. These reconstituted gene sets were generated based on similarity analysis from gene expression of 77,840 samples, manually curated gene-sets, molecular pathways from protein-protein interaction screening, and gene sets from mouse gene knock-out studies. Additionally, gene expression levels of from 37,427 human microarray samples are compiled in DEPICT and the tissue and cell types were mapped to 209 MeSH first level terms including physiological systems, tissues and cells. Enrichment of tissues and cell types was conducted by assessing whether urate-associated genes are highly expressed in the tissue and cell types.

All variants with urate association *P*-values <$1x10^{-5}$ from the trans-ethnic meta-analysis results were used as input. Independent SNPs were identified using PLINK 1.9[17] clump command within 500 kb flanking regions and r^2>0.1 in the 1000 Genomes phase1 version 3 data excluding the MHC region (chr6:25–35 Mb). False discovery rates (FDRs) were computed using 500 repetitions, and *P*-values were computed using 5,000 permutations from 500 null GWAS sets adjusting for gene length.

Affinity propagation clustering (APC)[18], implemented in the R package 'APCluster'[19], was applied to all reconstituted gene sets with FDR-corrected enrichment *P*-value <0.01 to cluster gene sets containing similar combinations of genes. Similarity between sets was assessed by the Z-scores of the top ten genes assigned to each gene set. The algorithm identifies a single reconstituted gene set from each cluster as an exemplar (meta gene set) that best represents the reconstituted gene sets within that cluster. A correlation matrix was calculated from the Z-scores of the top ten genes within the meta gene set. Correlations >0.2 were visualized as edges in a network in Cytoscape (http://cytoscape.org).

Stratified LD score regression for functional enrichment

Stratified LD score regression[20] estimates the SNP heritability of urate contributed by the SNPs linked to histone marks in each cell type. The enrichment of a category is defined as the proportion of SNP heritability in that cell type divided by the proportion of SNPs in the same cell type. Here, we assessed urate heritability enrichment in 10 cell types via stratified LD score regression with the EA-specific urate meta-analysis results as the input to match the ancestry of the LD score estimates. The 10 cell types were collapsed from 220 cell type-specific annotations for four histone marks: H3K4me1, H3K4me3, H3K9ac, and H3K27ac. Analyses were also carried out using trans-ethnic meta-analysis summary statistics as input and results were similar (data not shown).

Quality control of the UKBB sample used as to compute an LD reference panel for statistical fine-mapping

Fine-mapping based on summary statistics relies on LD estimates from an ancestry-matched reference panel whose sample size should scale with that of the GWAS[21]. Given the large sample size in the urate meta-analysis, we estimated LD from genotypes of 15,000 randomly

selected UKBB participants (Application ID 2027, Dataset ID 8974). As reported previously[22], we first removed individuals who withdrew consent, those with mismatched sex between self-reported and genetic, with genotype call rates <95%, outliers of variant heterozygosity or along the first two principal components from a principal component analysis seeded with the HapMap phase 3 release 2 populations. We retained only one member of each pair of individuals with pair-wise identity-by-descent statistic ≥0.1875. Altogether, 13,558 individuals with 16,969,363 SNPs were selected as the LD reference panel for fine-mapping.

Workflow for statistical fine-mapping

First, we combined neighboring loci with correlated index SNPs (r^2≥0.2) in the EA meta-analysis into discrete regions. Next, we performed stepwise model selection using GCTA (cojo-slct option) to identify independent index SNPs in each region. For regions with more than one independent index SNPs, we performed conditional analysis (GCTA cojo-cond option) to obtain conditional beta and standard errors. Approximate Bayes factors (ABF) were calculated using the Wakefield's formula[23], as implemented in the R package 'gtx' version 2.0.1 (https://github.com/tobyjohnson/gtx) using the conditional betas and standard errors for regions with multiple independent SNPs and the betas and standard errors of the original EA meta-analysis for regions with a single independent index SNP. The prior standard deviation was calculated as 0.061 based on formula (8) of the original publication of the Wakefield's formula [23] and the 95% interval of the SNP effect sizes in the EA meta-analysis. The posterior probability for a variant being the driver of the association signal was calculated as the ABF of the variant divided by the sum of the ABF in the region. The 99% credible sets of a region is derived by summing the posterior probabilities in descending order until the cumulative posterior probability was >99%. We prioritized variants in credible sets containing ≤5 SNPs or SNPs with posterior probabilities >0.5.

We compared the list of prioritized variants with results using the conditional mode in FINEMAP, an alternative approach for statistical fine-mapping.[24] We used the same prior standard deviation and EA meta-analysis summary statistics as input as those for the Wakefield method. The correlations between SNPs were based on the same UKBB reference panel as used in GCTA model selection and conditional analysis.

Trans-eQTL annotation

We performed *trans*-eQTL annotation for the 183 trans-ethnic index SNPs and their proxies (r^2 >0.8 in both the 1000 Genomes phase 3 European and East Asian reference panels) in eQTL studies with >1,000 individuals: the Framingham Heart Study[25], Westra et al.[26], Zeller et al.[27], Fehrmann et al.[28], and the LIFE Heart[29] and LIFE-Adult[30] studies. Westra *et al*. used whole blood from 5,257 individuals from the Framingham Heart Study and Affymetrix Human Exon 1.0ST expression-chip technology. Westra *et al*. is an eQTL-meta-analysis of nine datasets that used whole blood and Illumina HumanRef-8v2.0, Illumina HT12v3, or Illumina HT12v4 expression-chip technology. *Trans*-eQTL analysis of Westra *et al*. was restricted to previously reported GWAS SNPs. Fehrmann *et al*.[28] used whole blood from 1,469 individuals and Illumina HumanRef-8v2.0 and Illumina HT12v3 expression-chip technology. *Trans*-eQTL analysis of Fehrmann *et al*. was performed genome-wide. Fehrmann *et al*. was not regarded as an independent study in respect to Westra *et al.* as it was included in the meta-analysis of the latter. With respect to the other eQTL-studies, Fehrmann *et al*. is an independent study. Zeller *et al*[27]. used monocytes from 1,469 individuals and Illumina HT12v3 technology. LIFE Heart and LIFE Adult comprised an update of a previous eQTL-study[31] combining 4,285 peripheral blood mononuclear cell-samples from LIFE-Heart[321] and 2,360 whole-blood samples from LIFE-Adult[33] totaling 6,645 samples. Measurement and analysis of the combined data was done as previously described,[31] with the difference that FDR of the *trans*-eQTL from the LIFE Heart and LIFE Adult combined dataset was calculated after applying a hierarchical testing procedure based on Benjamini and Bogomolov[34] to avoid excess of false positives on the gene level. To account for differences between the LIFE Heart and LIFE Adult studies, a study identifier was included as a binary covariate in the regression model.

To improve stringency of results, we only report inter-chromosomal *trans*-eQTLs showing gene expression association *P*-values $<5x10^{-8}$ in at least two of the above mentioned independent samples. To characterize whether the identified *trans*-associated eQTL transcripts were enriched in any biological pathways, we conducted gene enrichment analysis using DOSE, an R/Bioconductor package for disease ontology semantic and enrichment analysis[35], as well as packages ReactomePA and clusterProfiler for enrichment analysis using the Human Disease Ontology database, GO, KEGG, and Reactom[4,36-39]. The background included all 19,327 protein-coding genes from Ensembl/Havana reported in Ensembl release 91.

Site-Directed Mutagenesis Primers

PAGE purified primers:

HNF1A-A98V-Forward: CCCTGAGGAGGCGGTCCACCAGAAAGCCG;

HNF1A-A98V-Reverse: CGGCTTTCTGGTGGACCGCCTCCTCAGGG;

HNF4A-T139I-Forward: GACCGGATCAGCATTCGAAGGTCAAGC;

HNF4A-T139I-Reverse: GCTTGACCTTCGAATGCTGATCCGGTC.

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RS The Rotterdam Study has been approved by the Medical Ethics Committee of the Erasmus MC (registration number MEC 02.1015) and by the Dutch Ministry of Health, Welfare and Sport (Population Screening Act WBO, license number 1071272-159521-PG). The Rotterdam Study has been entered into the Netherlands National Trial Register (NTR; www.trialregister.nl) and into the WHO International Clinical Trials Registry Platform (ICTRP; www.who.int/ictrp/network/primary/en/) under shared catalogue number NTR6831. All participants provided written informed consent to participate in the study and to have their information obtained from treating physicians. The generation and management of GWAS genotype data for the Rotterdam Study (RS I, RS II, RS III) was executed by the Human Genotyping Facility of the Genetic Laboratory of the Department of Internal Medicine, Erasmus MC, Rotterdam, The Netherlands. The GWAS datasets are supported by the Netherlands Organisation of Scientific Research NWO Investments (nr. 175.010.2005.011, 911-03-012), the Genetic Laboratory of the Department of Internal Medicine, Erasmus MC, the Research Institute for Diseases in the Elderly (014-93-015; RIDE2), the Netherlands Genomics Initiative (NGI)/Netherlands Organisation for Scientific Research (NWO) Netherlands Consortium for Healthy Aging (NCHA),

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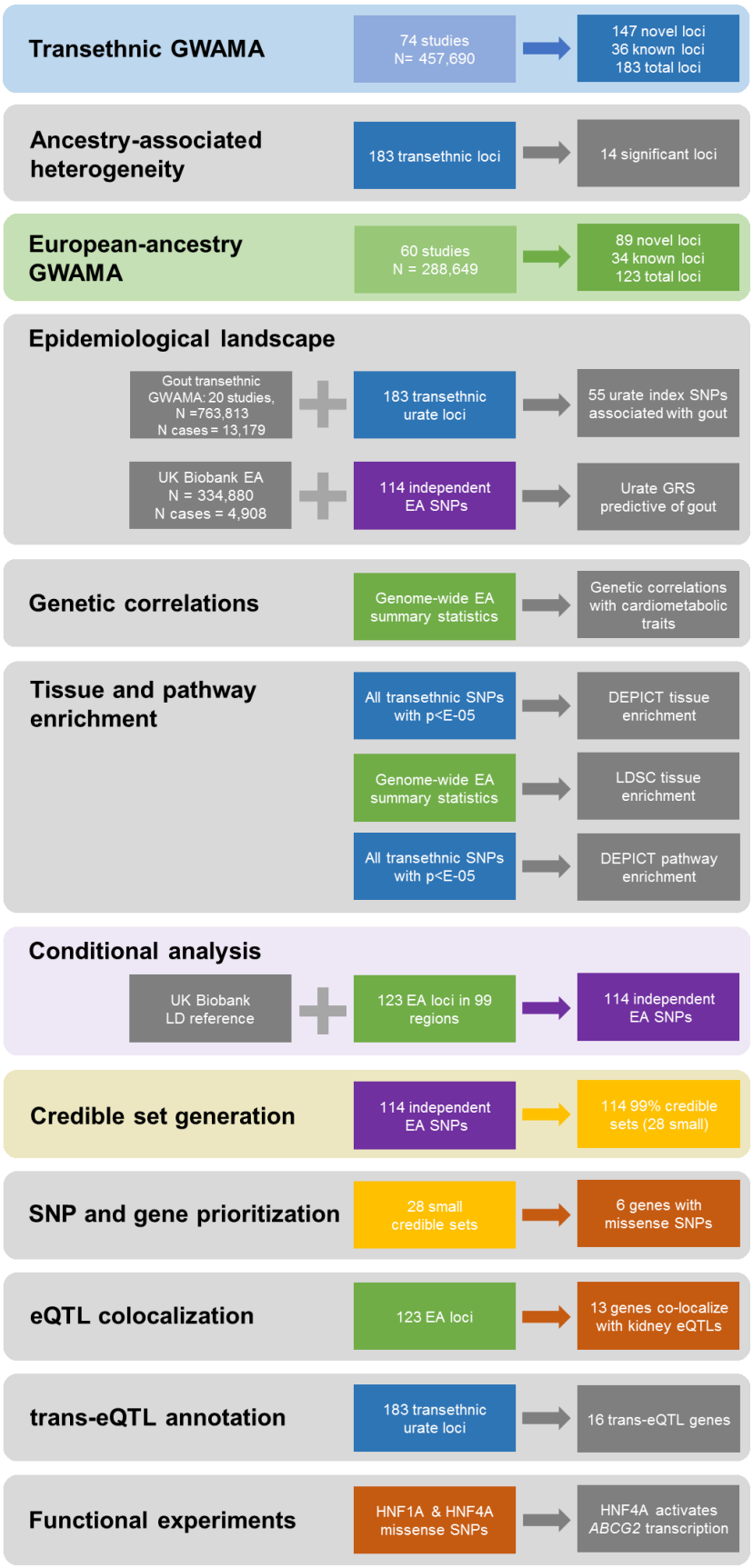
- White River Junction VA Medical Center (Brooks Robey)
- William S. Middleton Memorial Veterans Hospital (Robert Striker)

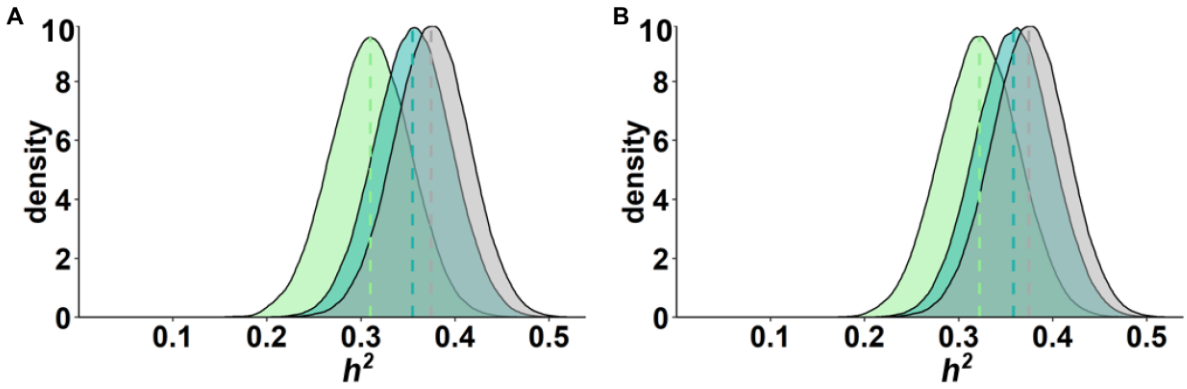
Supplementary Figure 1: Workflow of the project

Overview of the analysis workflow from trans-ethnic meta-analysis, gout risk prediction, genetic correlation, enrichment analyses, and statistical fine-mapping to functional study.



Supplementary Figure 2: Density plots of the heritability of serum urate estimated from the Cooperative Health Research in South Tyrol (CHRIS) study

Heritability of serum urate estimated from the Cooperative Health Research in South Tyrol (CHRIS) study (n=4,373 individuals in 186 pedigrees) using index SNPs from the trans-ethnic meta-analysis (A) and from the European-ancestry meta-analysis (B). Gray: overall heritability; blue: heritability after removing index SNPs in *SLC2A9*, *ABCG2*, and *SLC22A12*; green: heritability after removing all index SNPs in the present study.

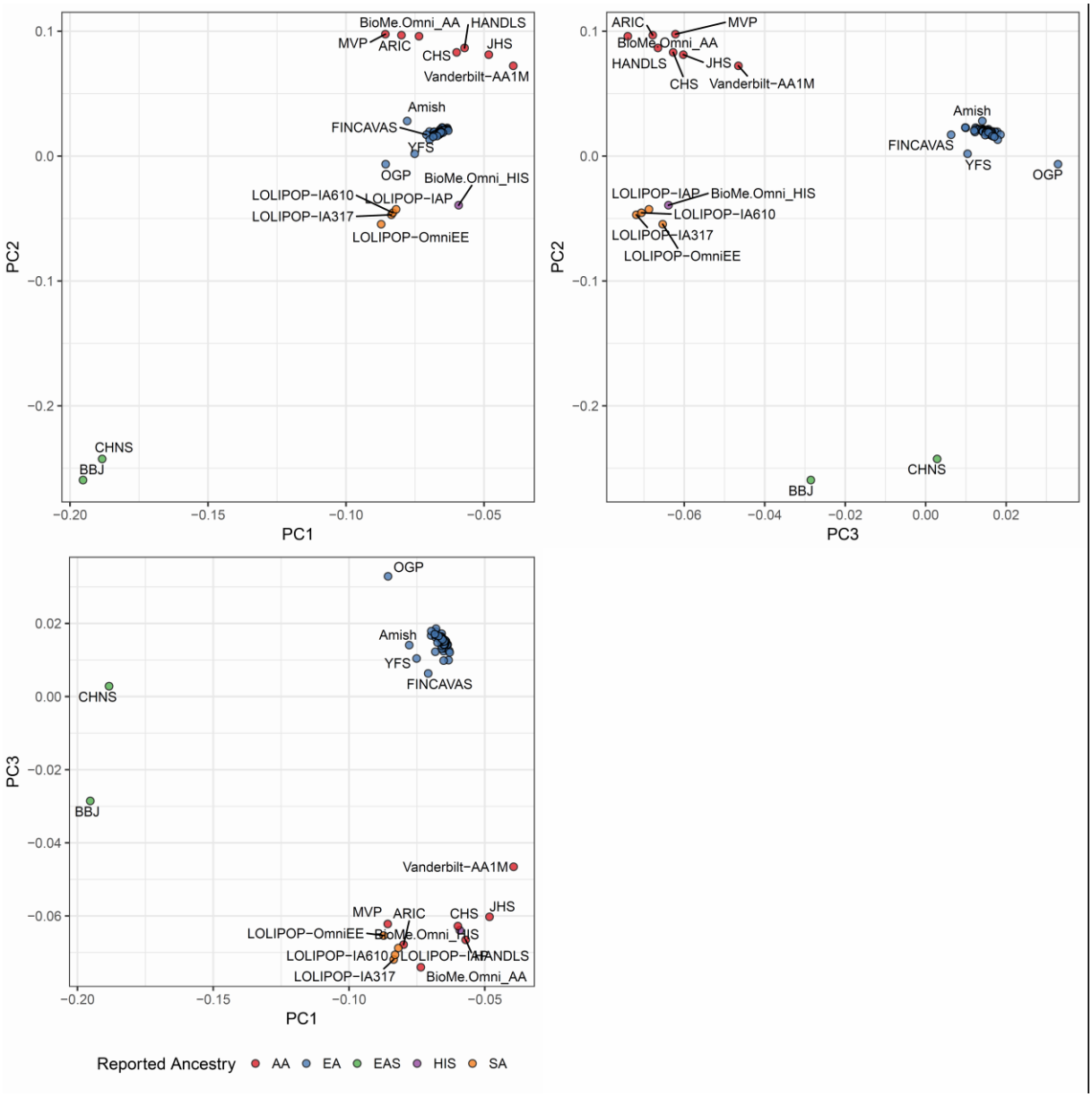


h2 (95% credible interval)	
Overall:	0.37 (0.29-0.45)
Without SNPs in 3 major loci:	0.35 (0.28-0.43)
Without all index SNPs:	0.31 (0.23-0.39)

h2 (95% credible interval)	
Overall:	0.37 (0.30-0.45)
Without SNPs in 3 major loci:	0.36 (0.28-0.44)
Without all index SNPs:	0.32 (0.24-0.40)

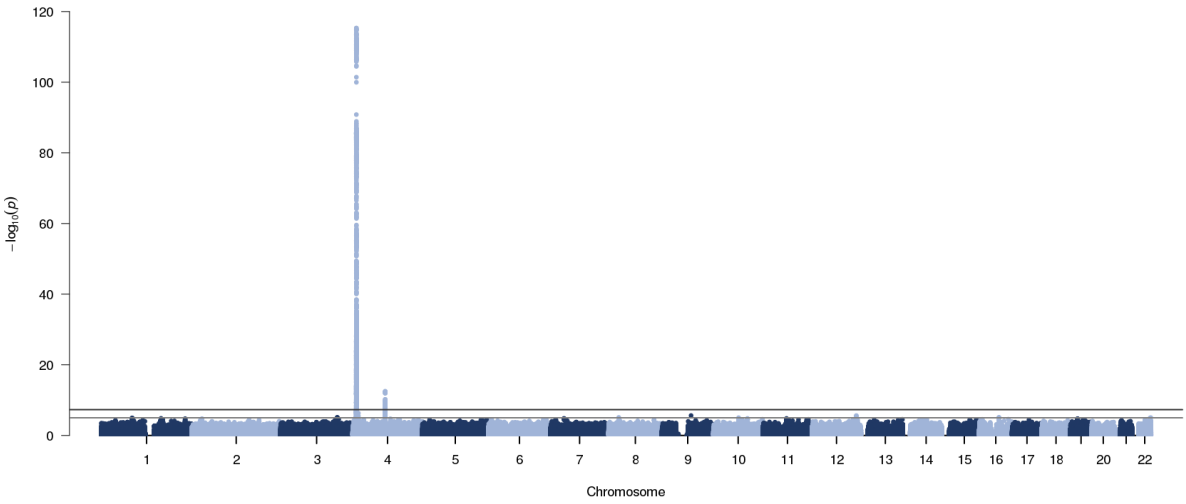
Supplementary Figure 3: Principal components generated using the mean allele frequency difference between studies.

Principal components (PCs) are generated using MR-MEGA from a matrix of mean pairwise allele frequency differences between cohorts (total n=457,690). Color denotes self-reported ancestry for each cohort. Selected outliers are labeled with cohort name. Three PCs were chosen as per author recommendations, and, as shown, are sufficient to separate self-reported ancestry groups.



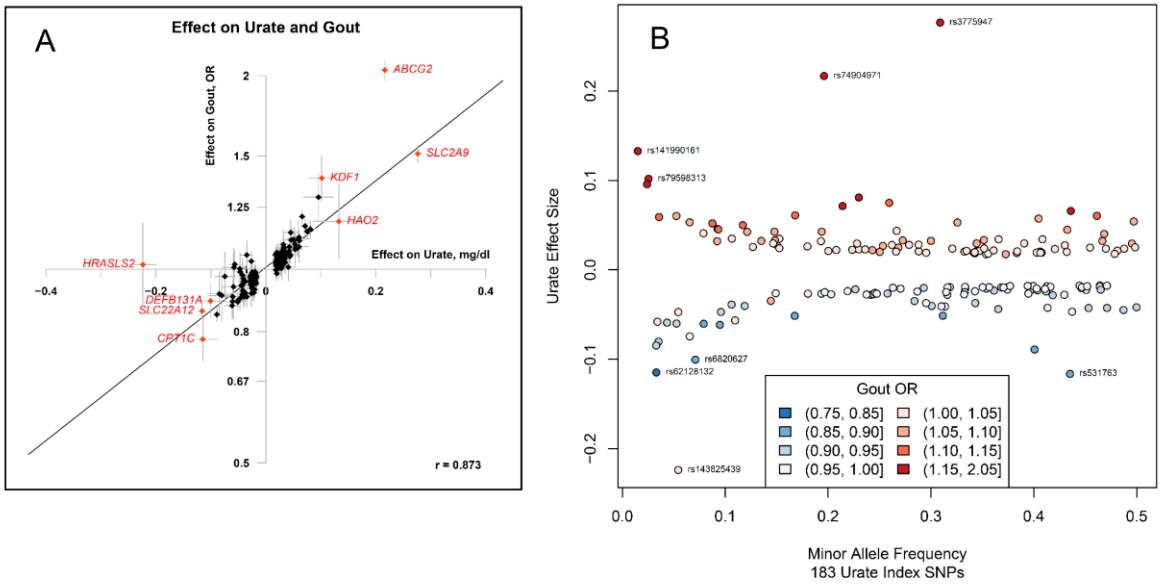
Supplementary Figure 4: Manhattan plot of the *P*-values of the differences in genetic effects on serum urate from trans-ethnic, sex-stratified meta-analyses.

GWAS of 174,111 men and 172,102 women were run separately and the effect sizes compared. *P*-values were obtained from a two-sample two-sided t-test for significant difference of association between men and women using the formula $t = \frac{\beta_M - \beta_F}{\sqrt{SE_M{}^2 + SE_F{}^2}}$, where β_M and β_F were beta coefficients among males and females, respectively, and SE_M and SE_F were the corresponding standard errors.



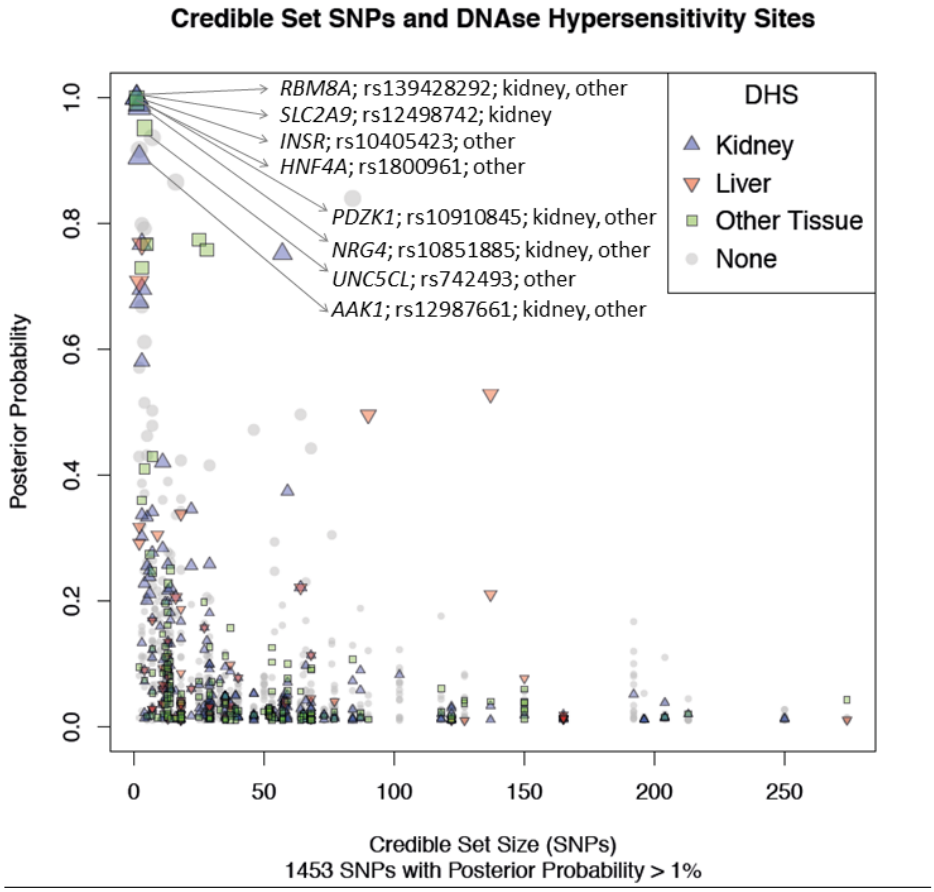
Supplementary Figure 5: Effect size of serum urate loci relating to gout (A) and minor allele frequency (B).

The effect sizes for serum urate and gout are represented by the index SNPs from the trans-ethnic meta-analysis of serum urate (n=457,690) and gout (n=763,813), respectively. The whiskers in (A) represent 95% confidence intervals and r is the Pearson correlation coefficient.



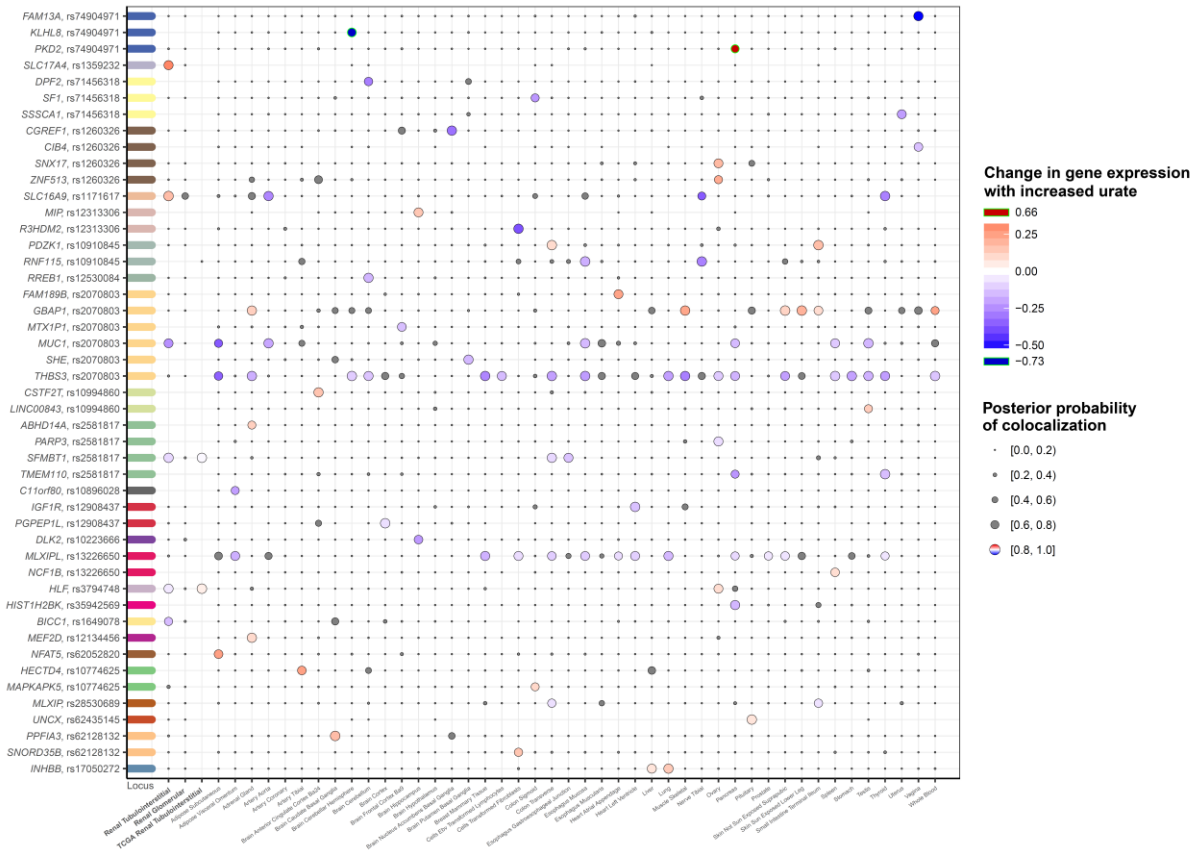
Supplementary Figure 6: Posterior probability of SNPs in 99% credible set with DNAse I hypersensitivity site annotation

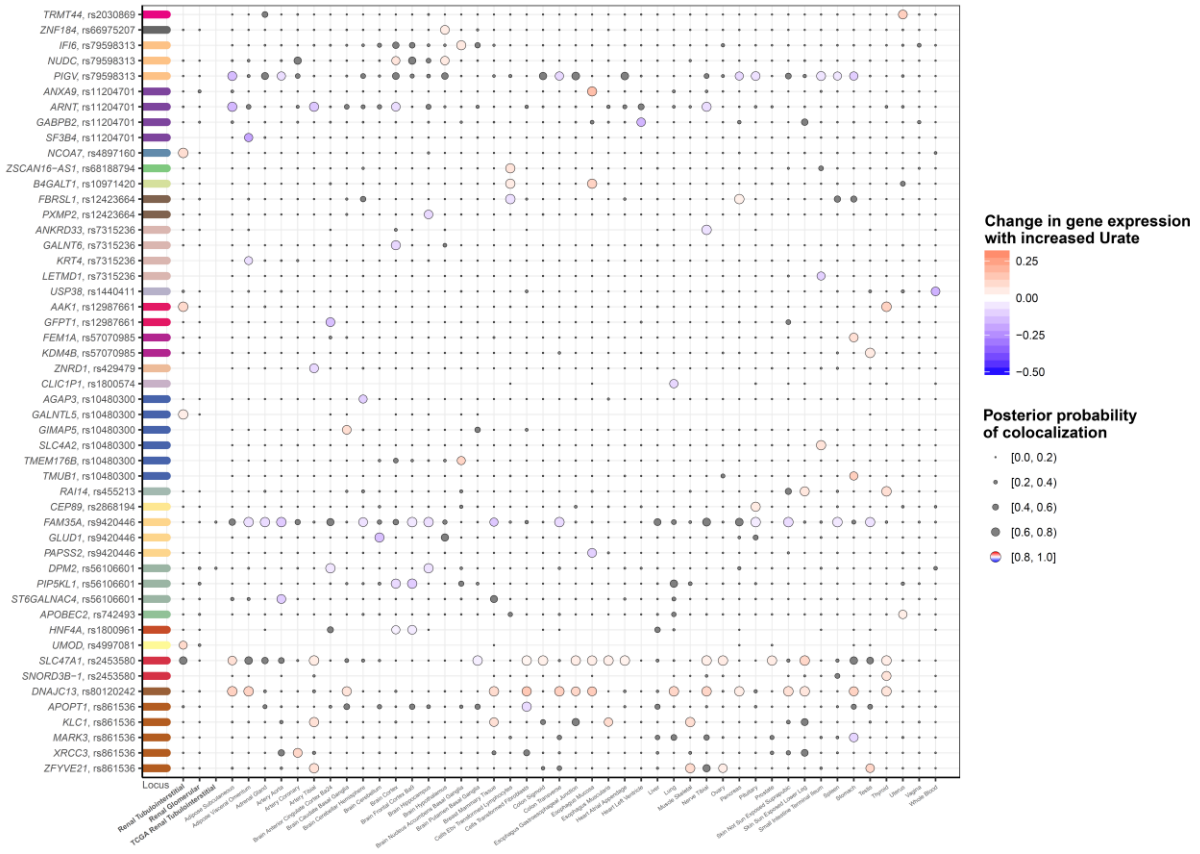
Graph shows credible set size (X-axis) against the posterior probability of association (PPA; Y-axis) for each of 1,453 SNPs with PPA >1% in 114 99% credible sets. SNPs mapping into ENCODE or RoadMap DNAse I hypersensitivity sites are highlighted.



Supplementary Figure 7: Co-localization of urate-association signals with gene expression in *cis* across 47 tissues

The plot shows genes whose expression levels in any tested tissues co-localized with the urate association signal with a posterior probability of ≥80%. Genes and their respective index SNP are shown on the Y-axis. The color adjacent to the SNP identifier on the Y-axis groups co-localization signals from one locus and helps to rapidly identify loci in which the urate association signal co-localizes with the expression of more than one gene. Co-localization across tissues (X-axis) is illustrated as dots, where the size of the dots indicates the posterior probability of the co-localization. The change in urate levels is color-coded relative to the change in gene expression with a color gradient as indicated in the legend, or gray in case of a posterior probability <0.80. Kidney tissues are labeled in bold.

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KDM4B, rs57070985
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CEP89, rs2868194
FAM35A, rs9420446
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PAPSS2, rs9420446
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KLC1, rs861536
MARK3, rs861536
XRCC3, rs861536
ZFYVE21, rs861536
Locus
Renal Tubulointerstitial
Renal Glomerular
TCGA Renal Tubulointerstitial
Change in gene expression with increased Urate
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−0.50
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[0.4, 0.6)
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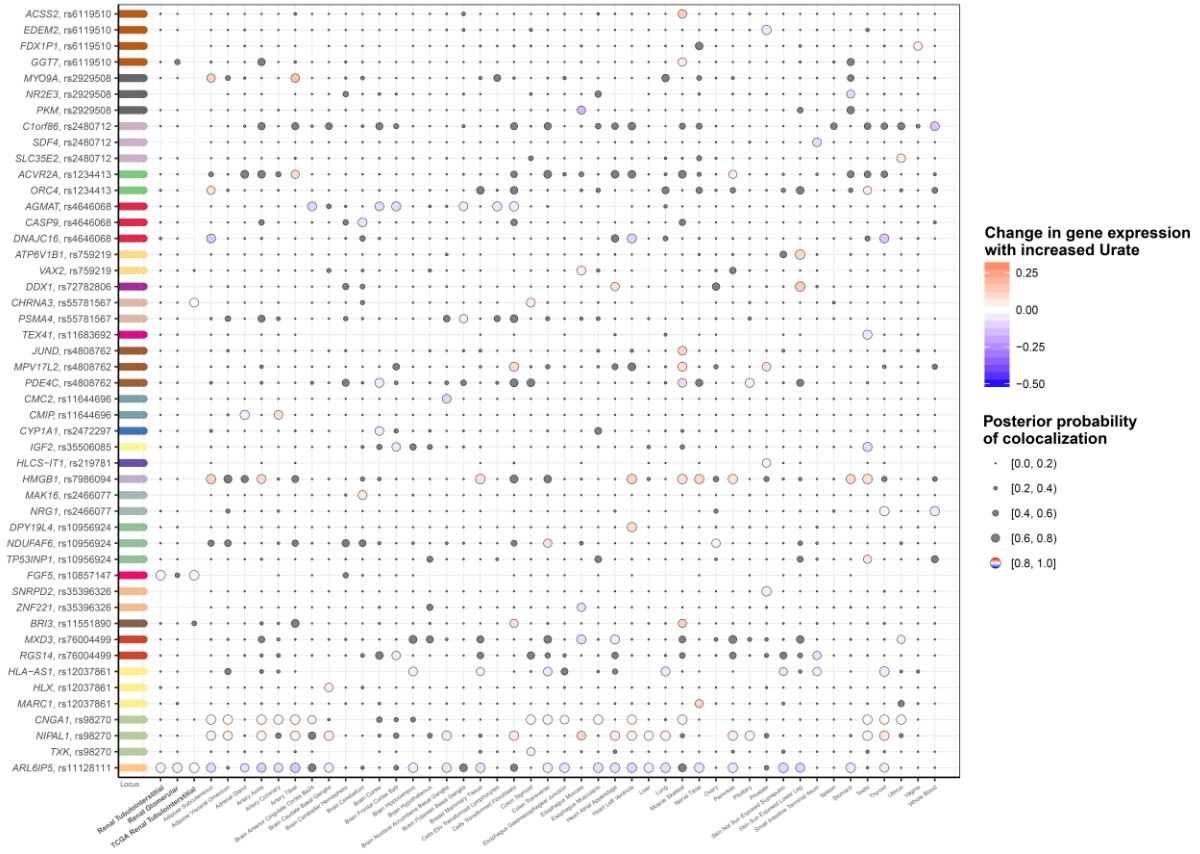
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ORC4, rs1234413
AGMAT, rs4646068
CASP9, rs4646068
DNAJC16, rs4646068
ATP6V1B1, rs759219
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DDX1, rs72782806
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JUND, rs4808762
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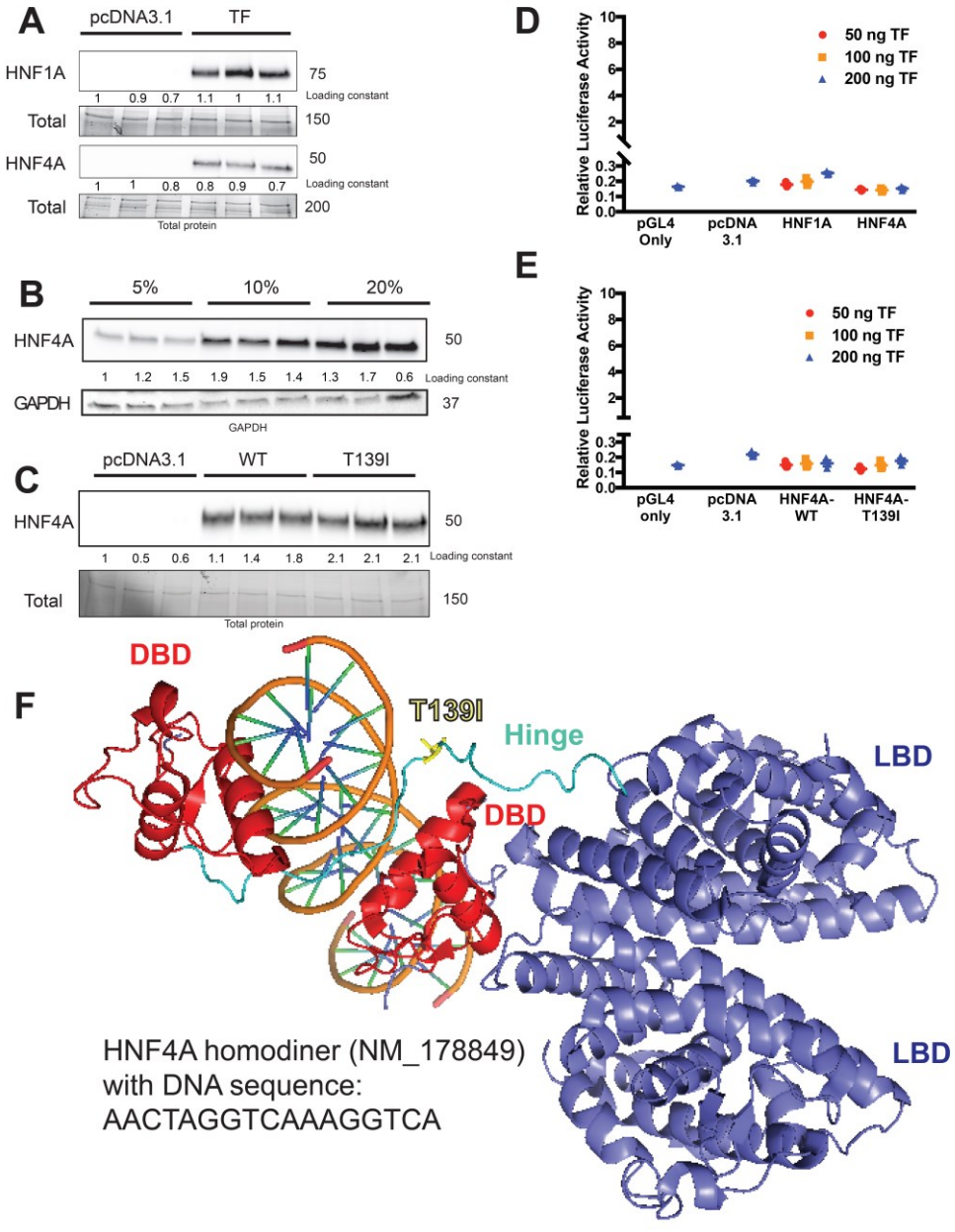
CYP1A1, rs2472297
IGF2, rs35506085
HLCS−IT1, rs219781
HMGB1, rs7986094
MAK16, rs2466077
NRG1, rs2466077
DPY19L4, rs10956924
NDUFAF6, rs10956924
TP53INP1, rs10956924
FGF5, rs10857147
SNRPD2, rs35396326
ZNF221, rs35396326
BRI3, rs11551890
MXD3, rs76004499
RGS14, rs76004499
HLA−AS1, rs12037861
HLX, rs12037861
MARC1, rs12037861
CNGA1, rs98270
NIPAL1, rs98270
TXK, rs98270
ARL6IP5, rs11128111
Locus
Renal Tubulointerstitial
Renal Glomerular
TCGA Renal Tubulointerstitial
Change in gene expression with increased Urate
0.25
0.00
−0.25
−0.50
Posterior probability of colocalization
[0.0, 0.2)
[0.2, 0.4)
[0.4, 0.6)
[0.6, 0.8)
[0.8, 1.0]

Supplementary Figure 8: Mechanics and mechanisms of *ABCG2* promoter luciferase assay (**A**) Expression of HNF1A and HNF4A in HEK 293 cells used for the luciferase *ABCG2* promoter activation assay demonstrating the successful transfection of the assay cells (n=3 for each treatment group). (**B**) Western blot of HNF4A showing that the resulting dose progression of HNF4A protein reflects the increasing dose of DNA used in the transfection of the HEK 293 cells; with GAPDH as loading control (from the same samples used in Figure 5C; n=3 for each treatment group). (**C**) The mutant HNF4A, T139I, expressed at comparable levels to wild-type in HEK 293 cells (from the same samples used in Figure 5E; n=3 for each treatment group). (**D & E**) Control experiments for the luciferase assay in Figure 5C and E: HEK293 cells transfected with an empty vector show no increase in luciferase activity (± SEM) from the same n=3 independent experiments as in Figure 5C & 5E. (**F**) Entire homodimer HNF4A structural model partially depicted in Figure 5D): location of mutation and relevant domains are identified (PBD 4IQR).



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