Genome-wide association analyses identify 18 new loci associated with serum urate concentrations

Supplementary Information

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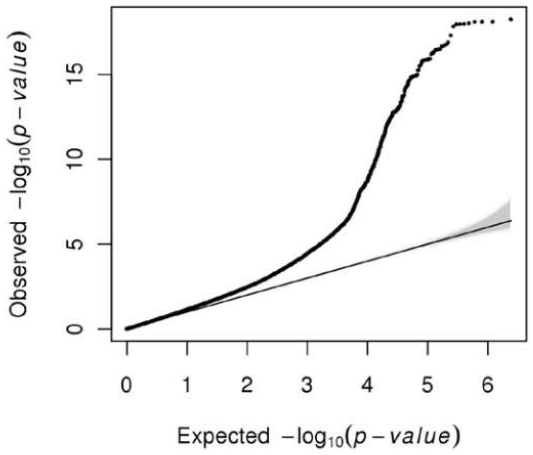
Supplementary Figures

Supplementary Figure 1: QQ Plot for Serum Urate GWAS

Quantile-quantile plot showing observed p-values of the urate meta-analysis vs. expected p-values by chance after removal of SNPs within +/- 1.5 Mb of the index SNP in *SLC2A9* and +/- 1 Mb of the index SNPs at 9 additional known urate-associated loci. A second genomic control step was applied to correct for the post meta-analysis of =1.12.



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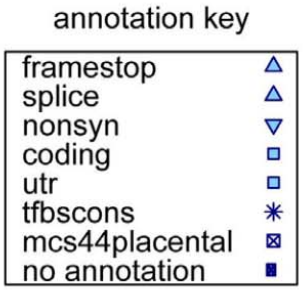
Supplementary Figure 2: Regional Association Plots

Regional association plot showing $-\log_{10}$ (p-values) for all SNPs ordered by their chromosomal position within all regions reaching p-values $<1*10^{-6}$ in the discovery screen of the overall or sex-stratified urate GWAS as well as the candidate urate transporter gene region. For sex-specific loci, $-\log_{10}$ (p-values) correspond to the respective sex-stratified urate GWAS. Each SNP is colored according to its correlation with the SNP showing the lowest p-value (index SNP) within the region as specified in the color scheme. Correlation structures correspond to HapMap 2 CEU r28. Gray color indicates unknown correlation. Data point symbols correspond to nonsense, non-synonymous, coding, UTR, splice variants, transcription factor binding sites and multi-species conservation according to dbSNP or the 1000 Genomes Project (August 2009 release)[1]. Plots are ordered by rs-number.



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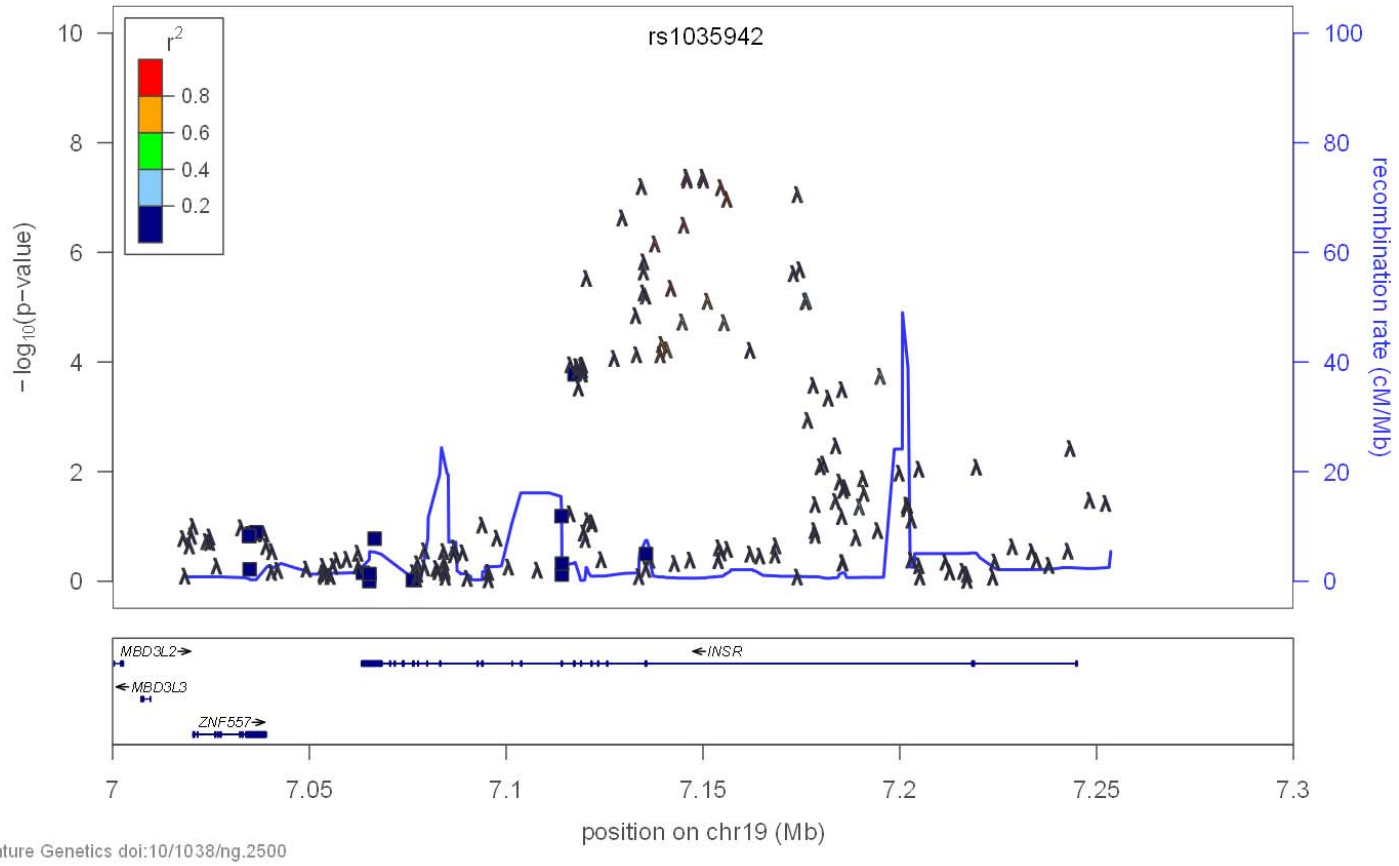

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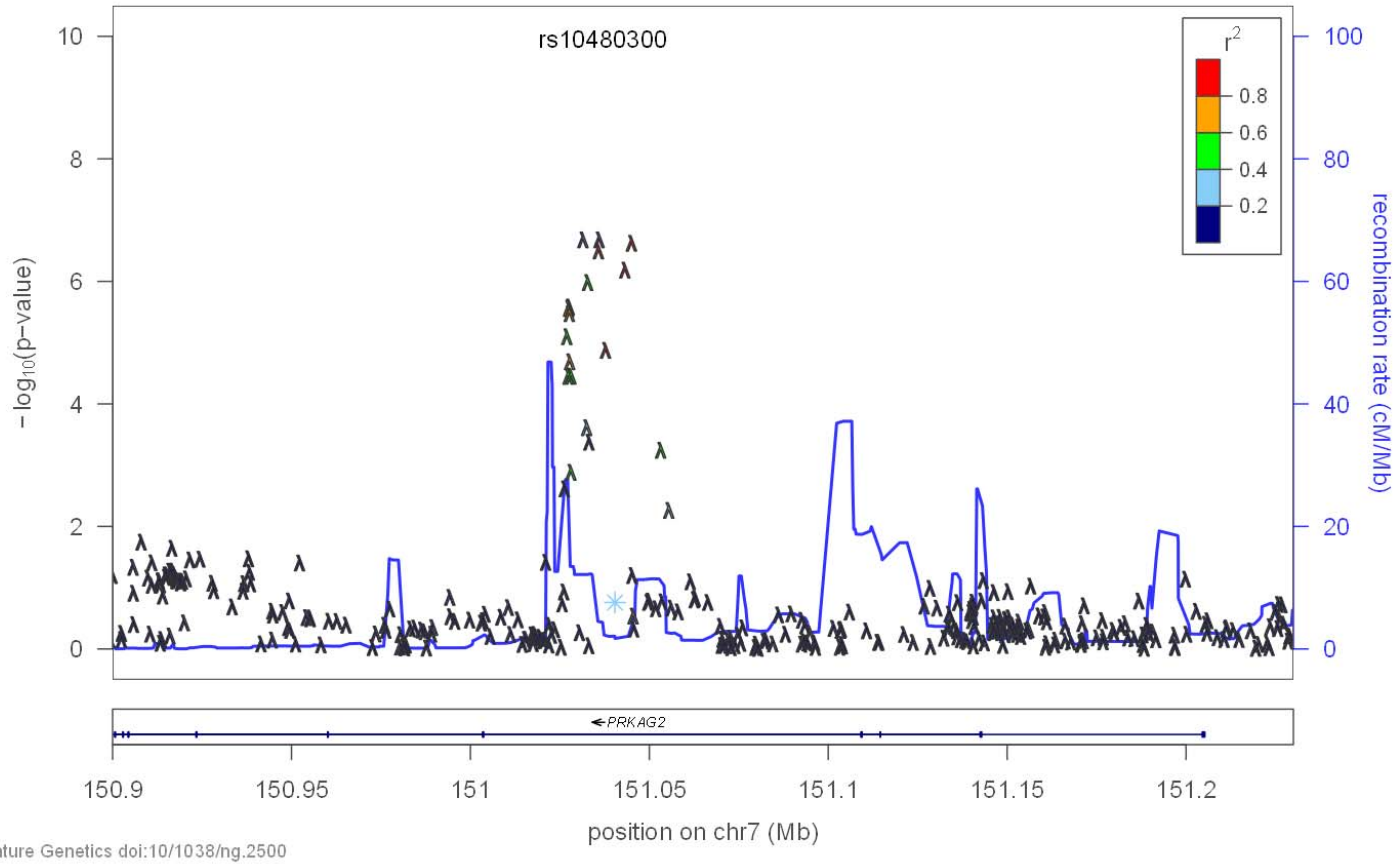

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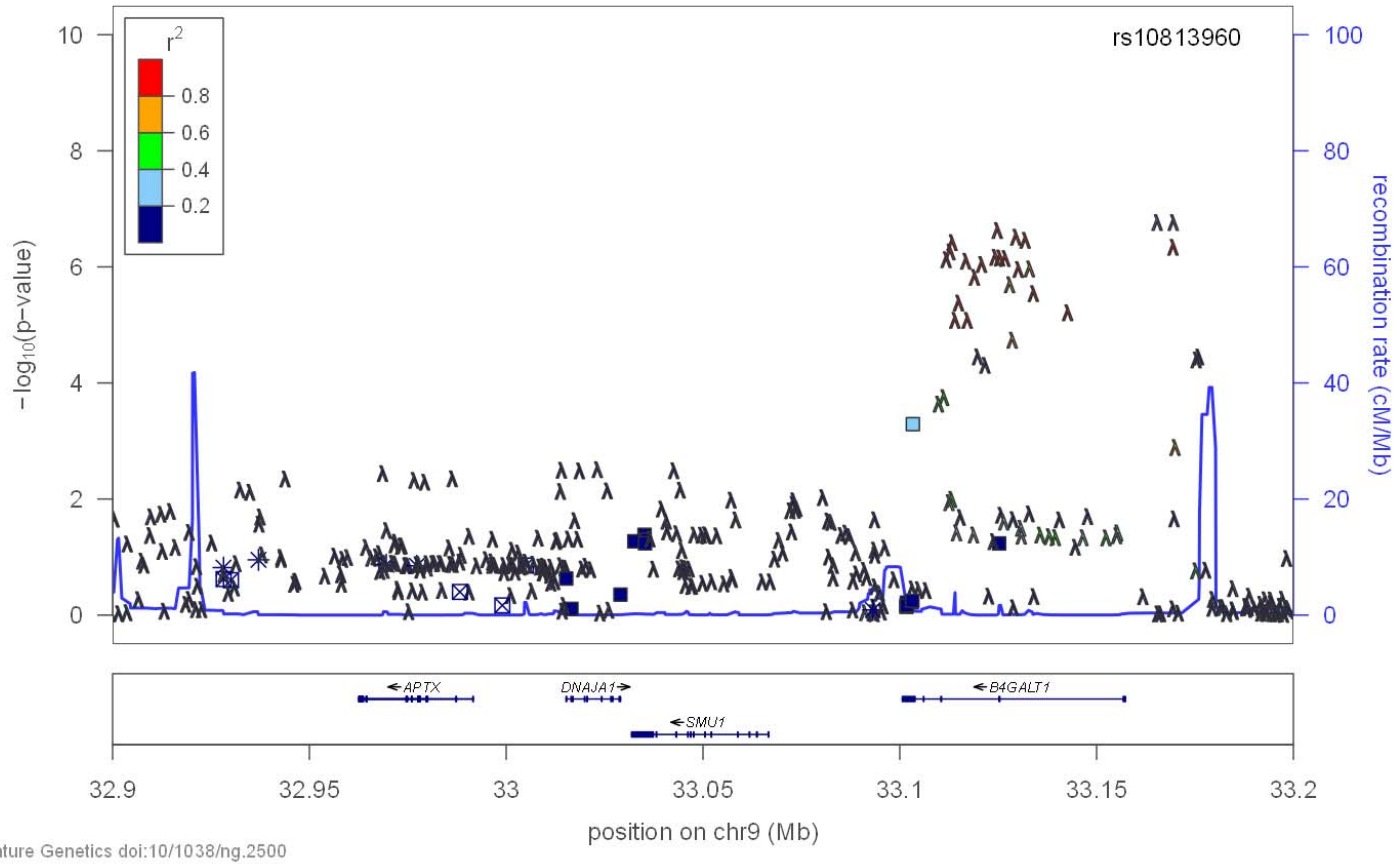

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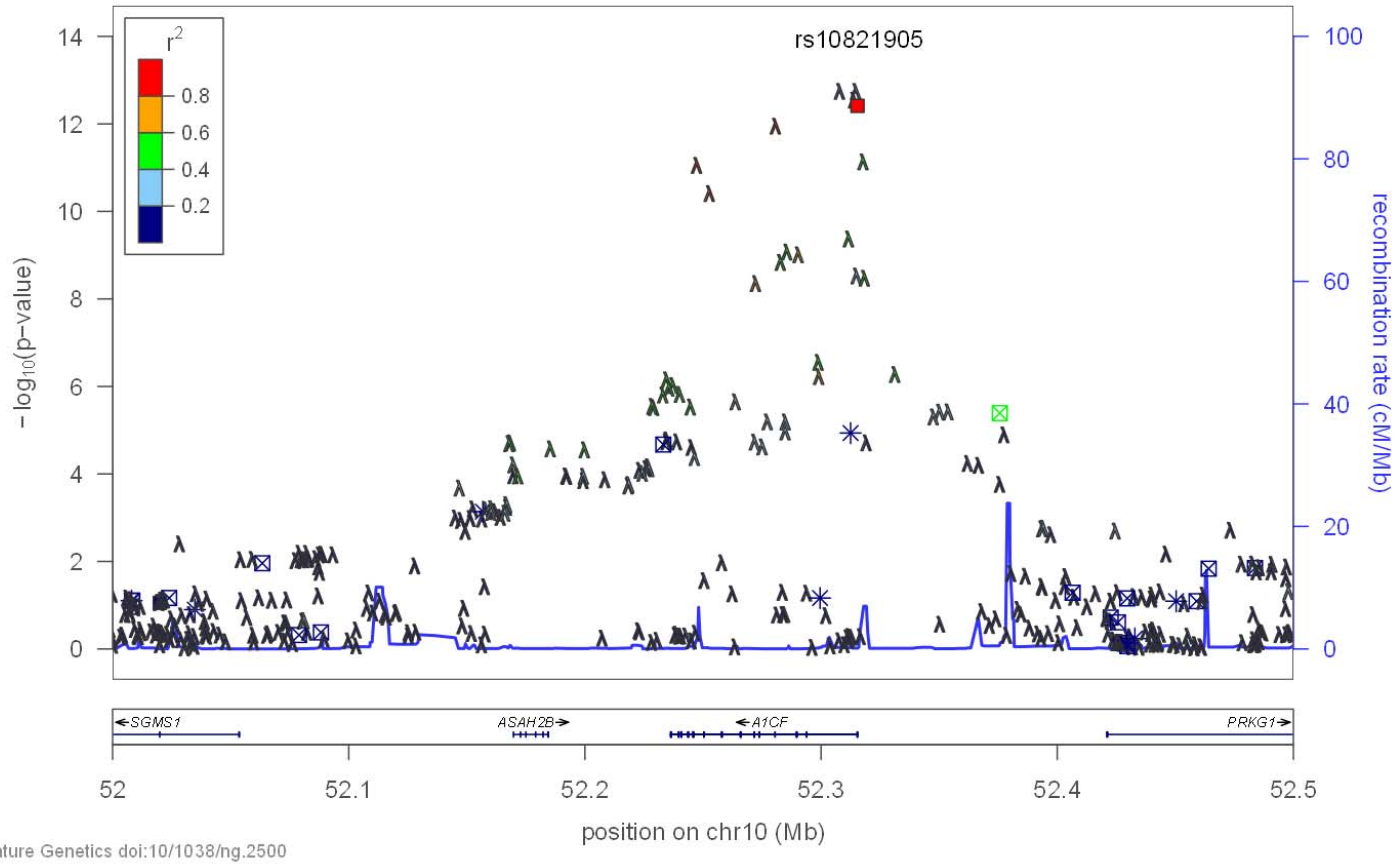

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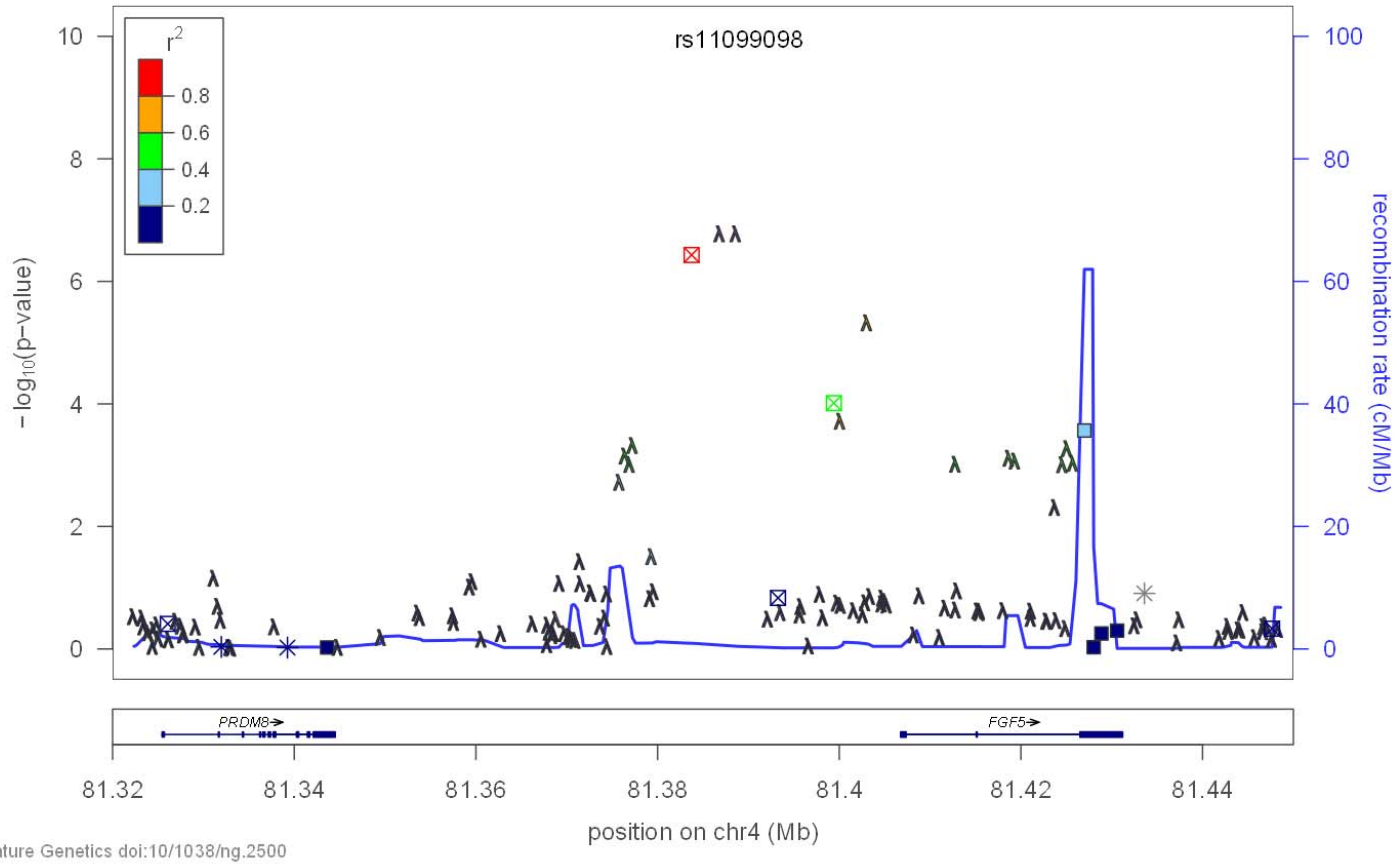

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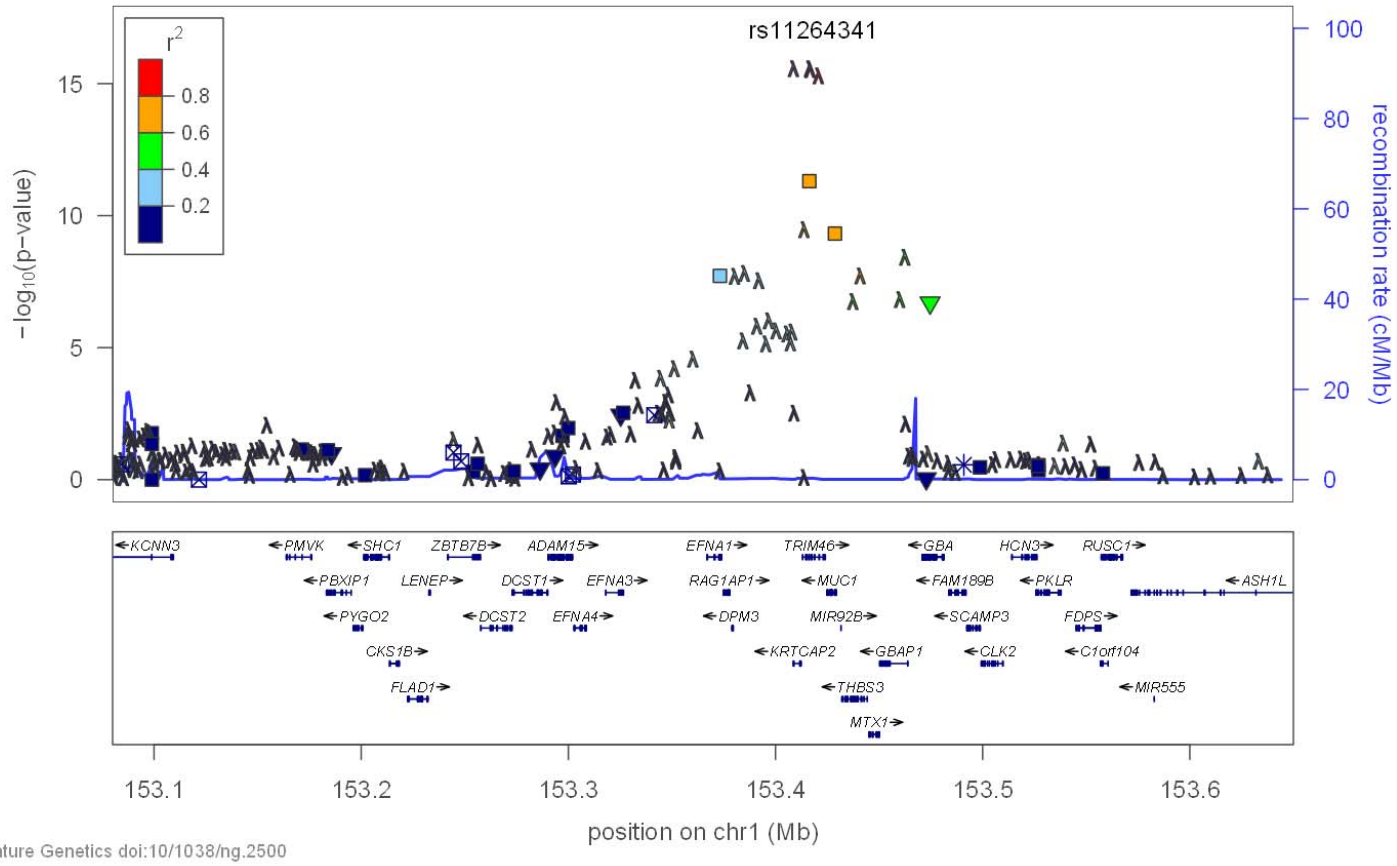

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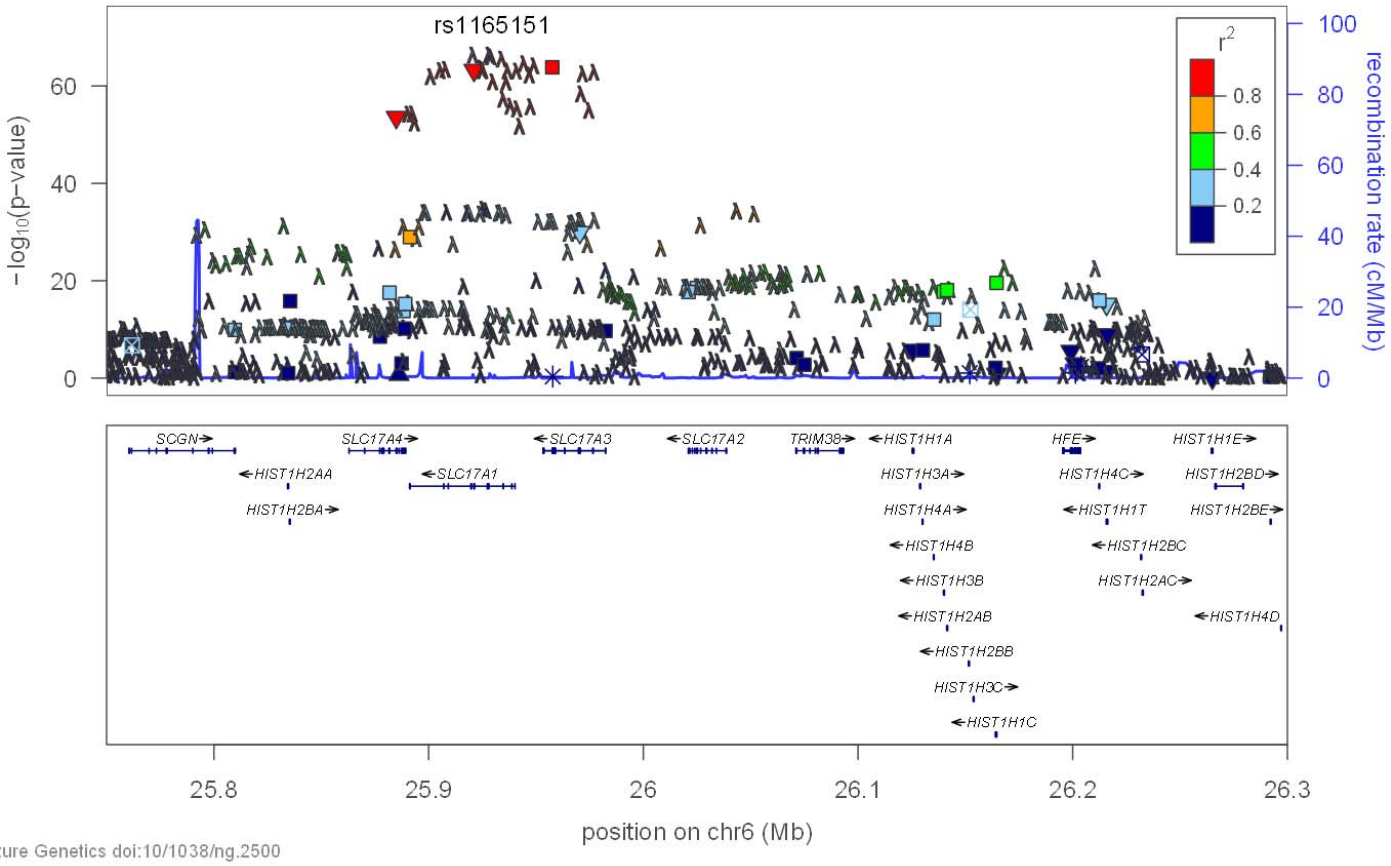

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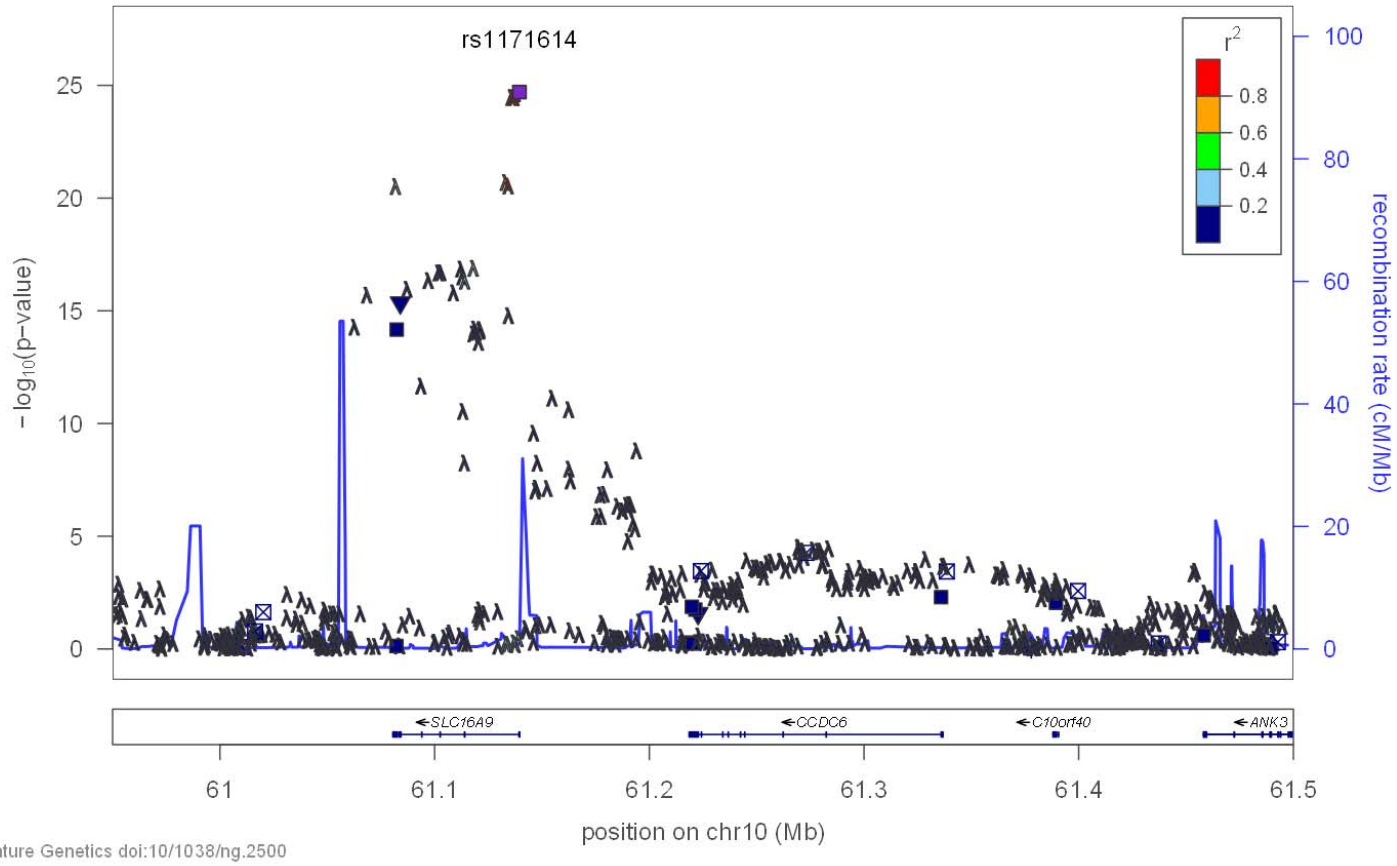

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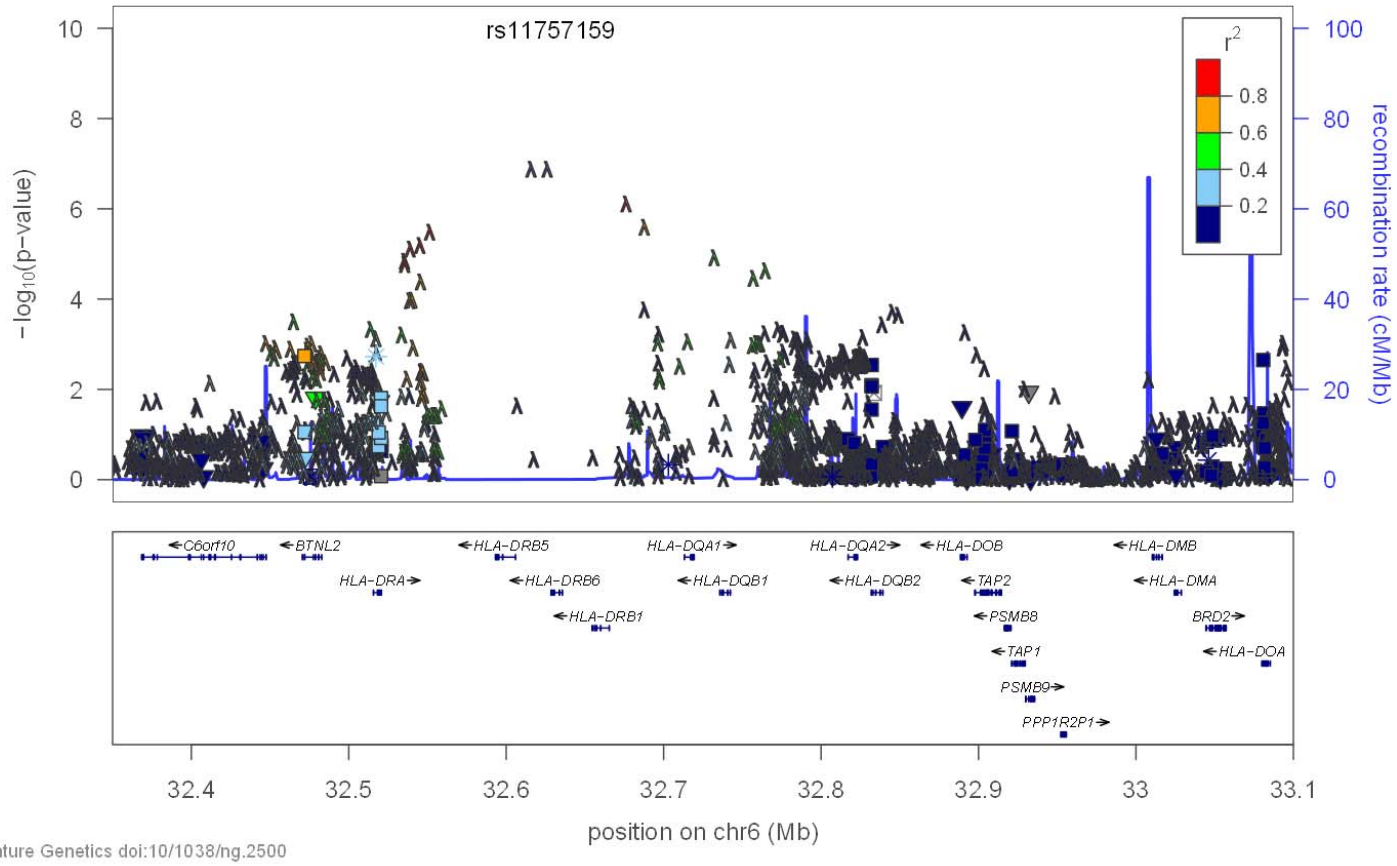

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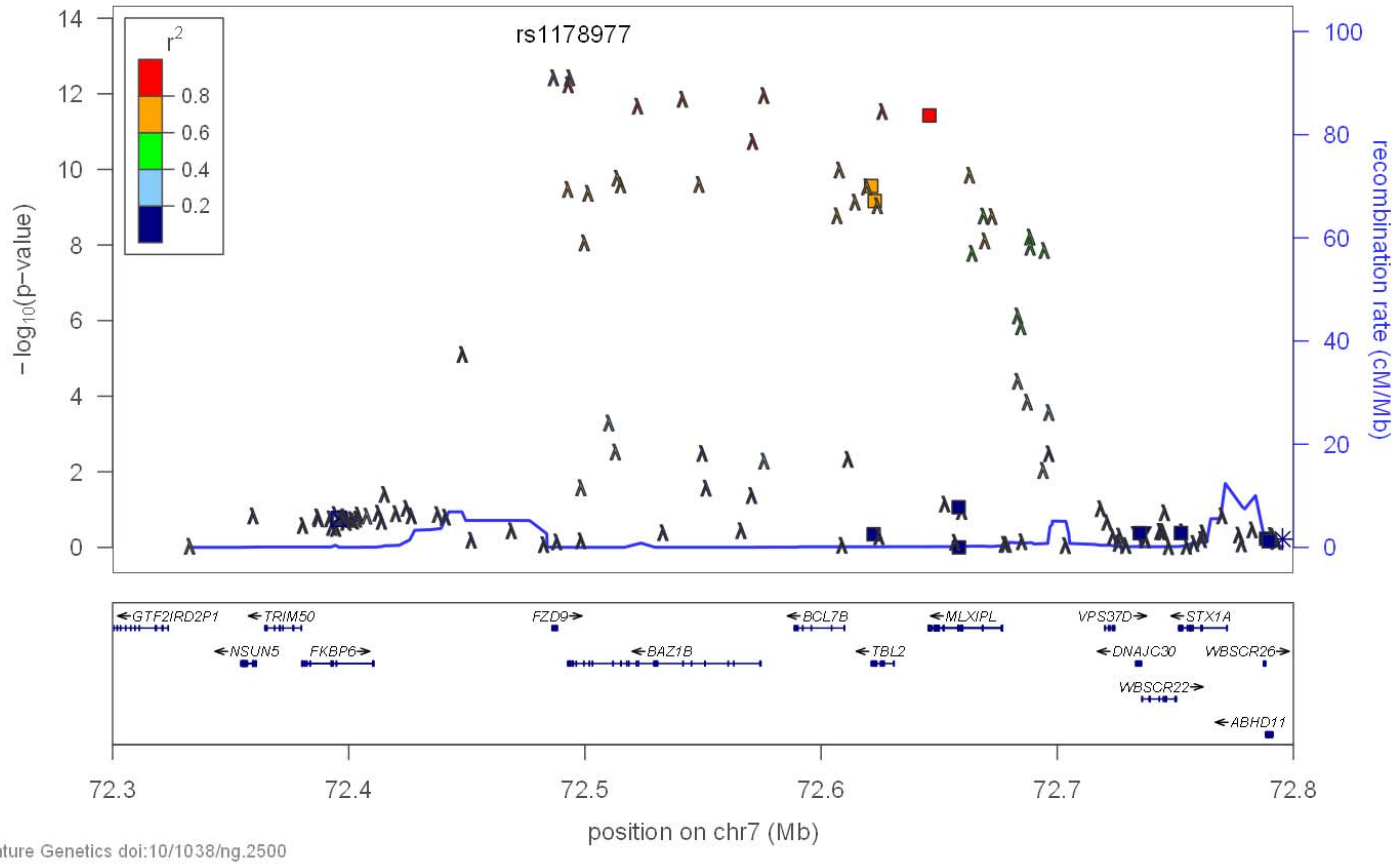

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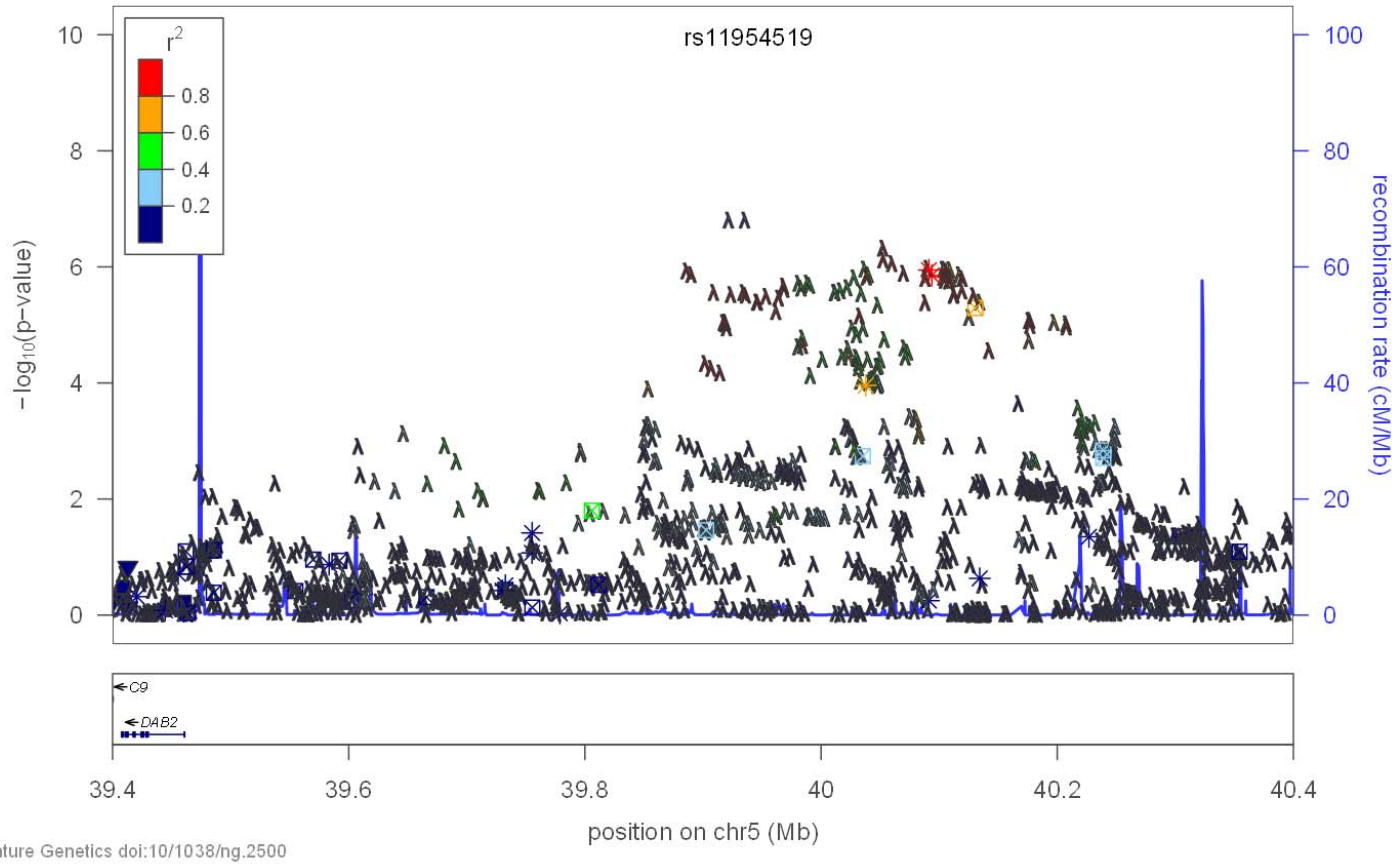

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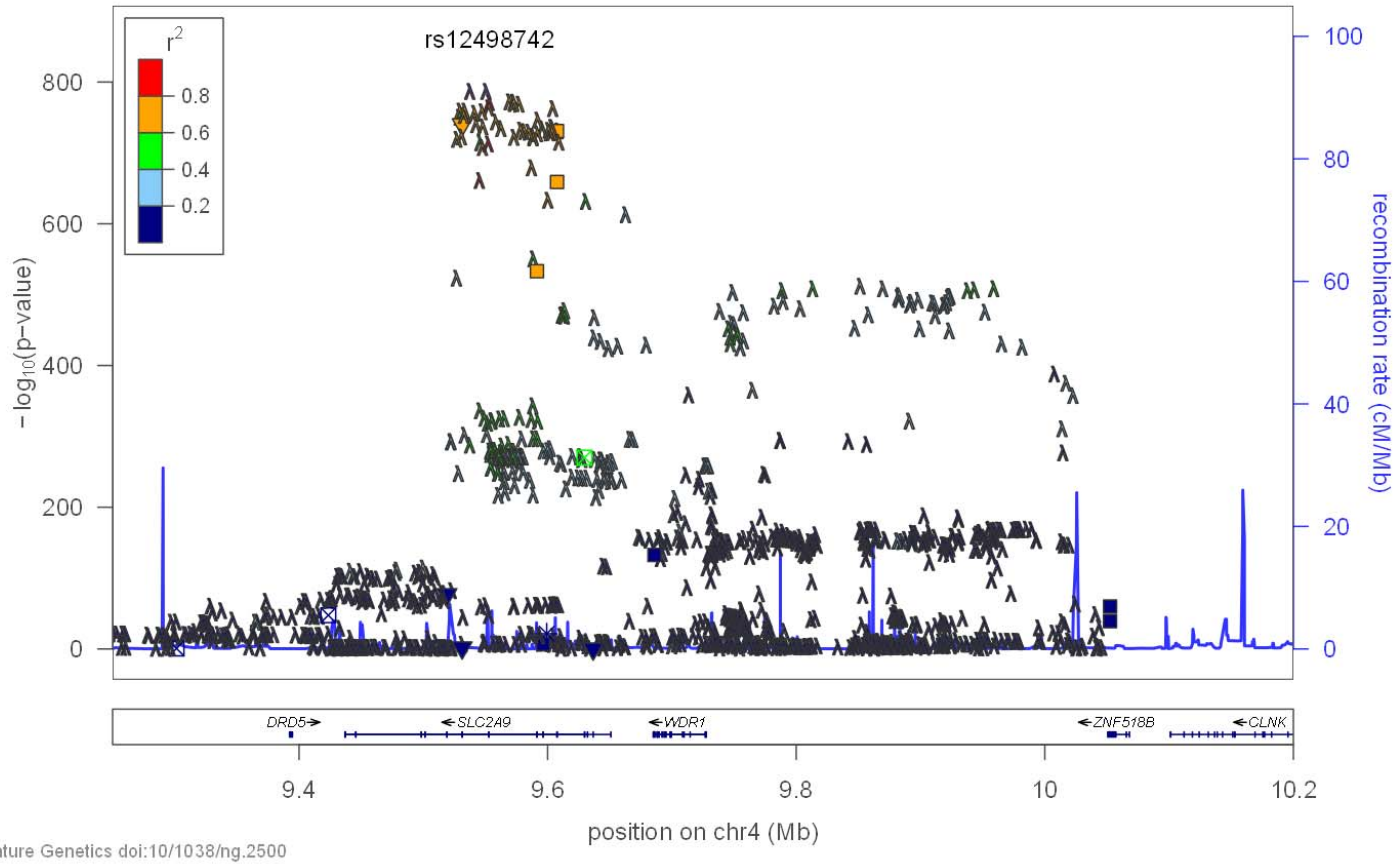

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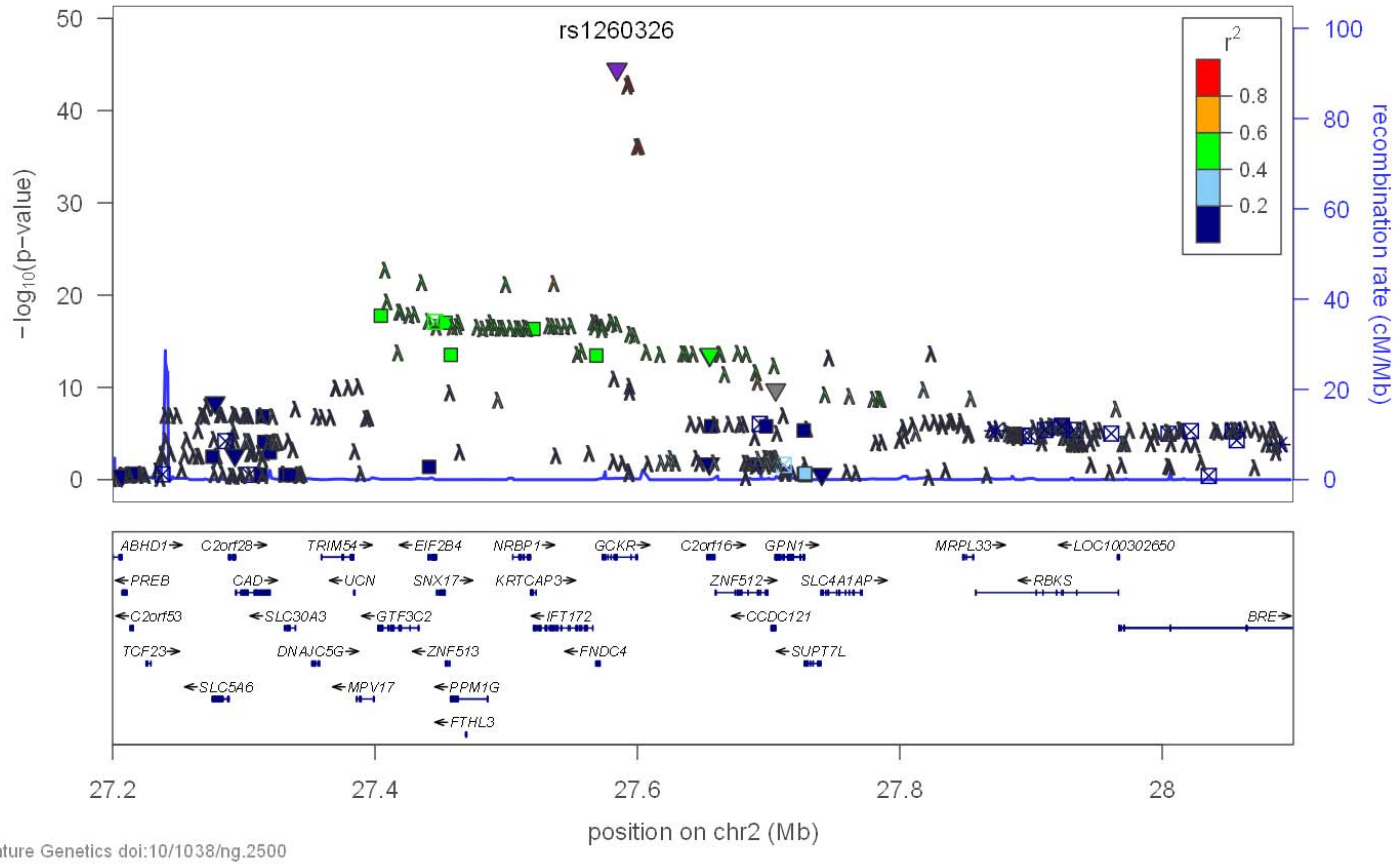

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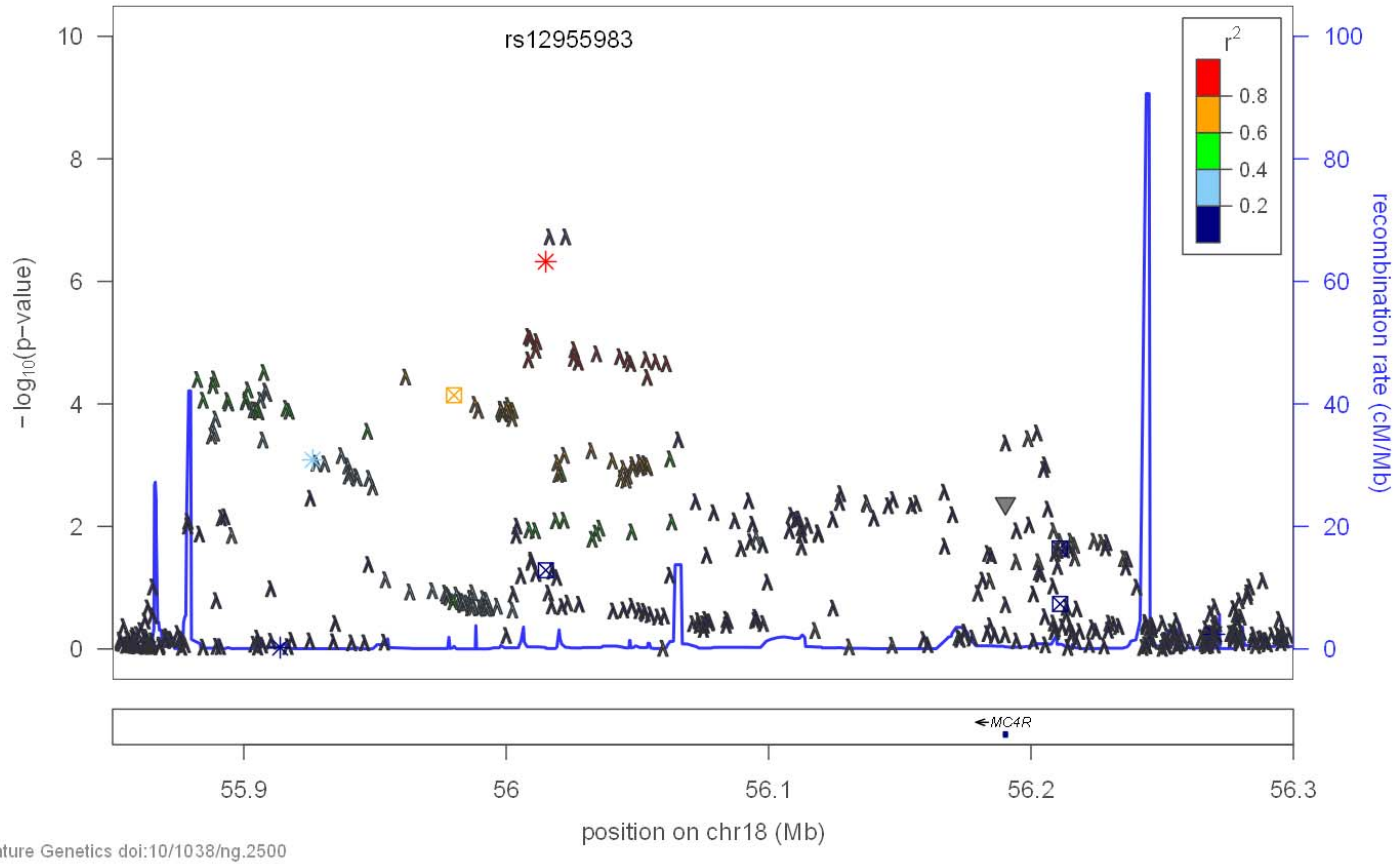

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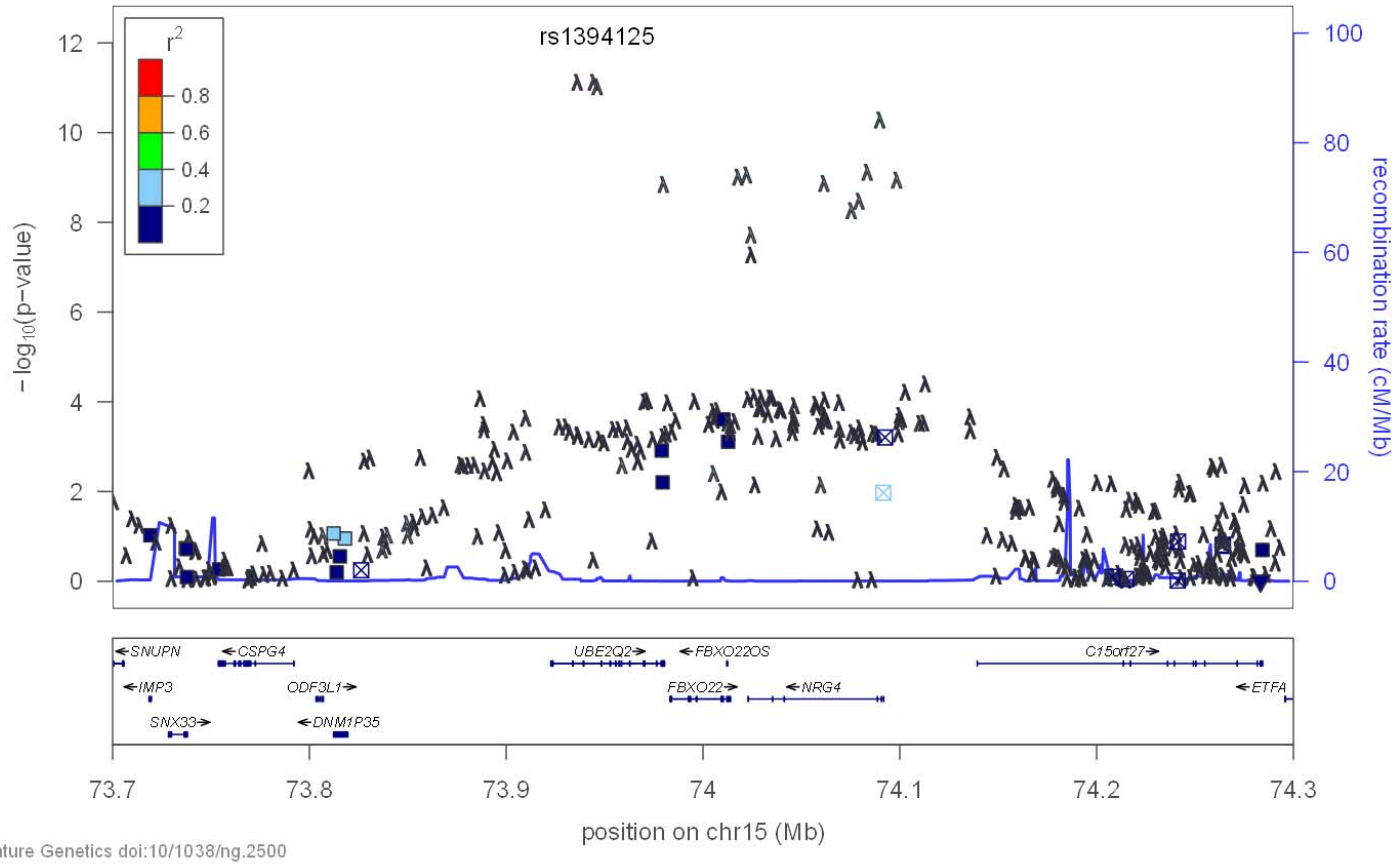

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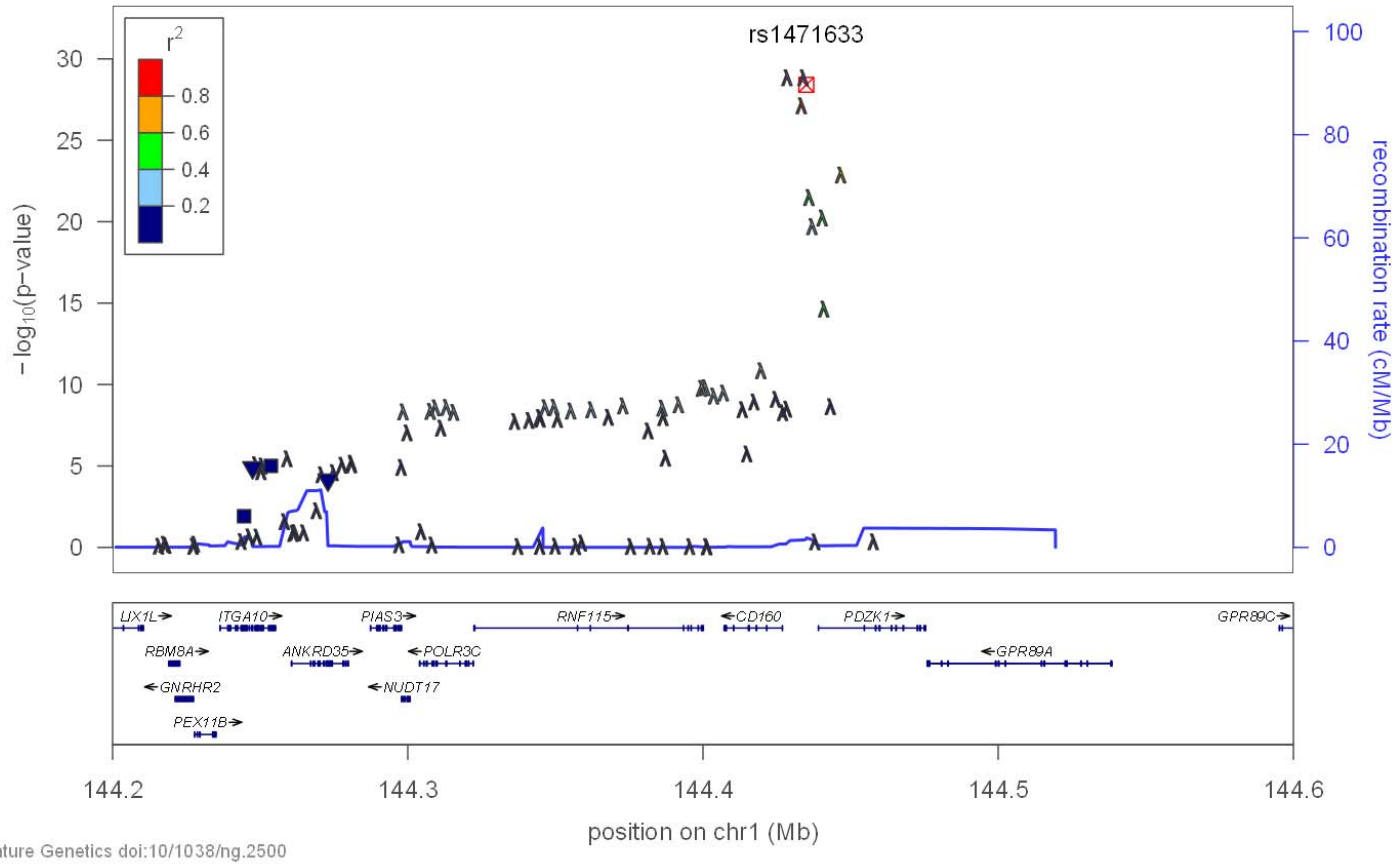

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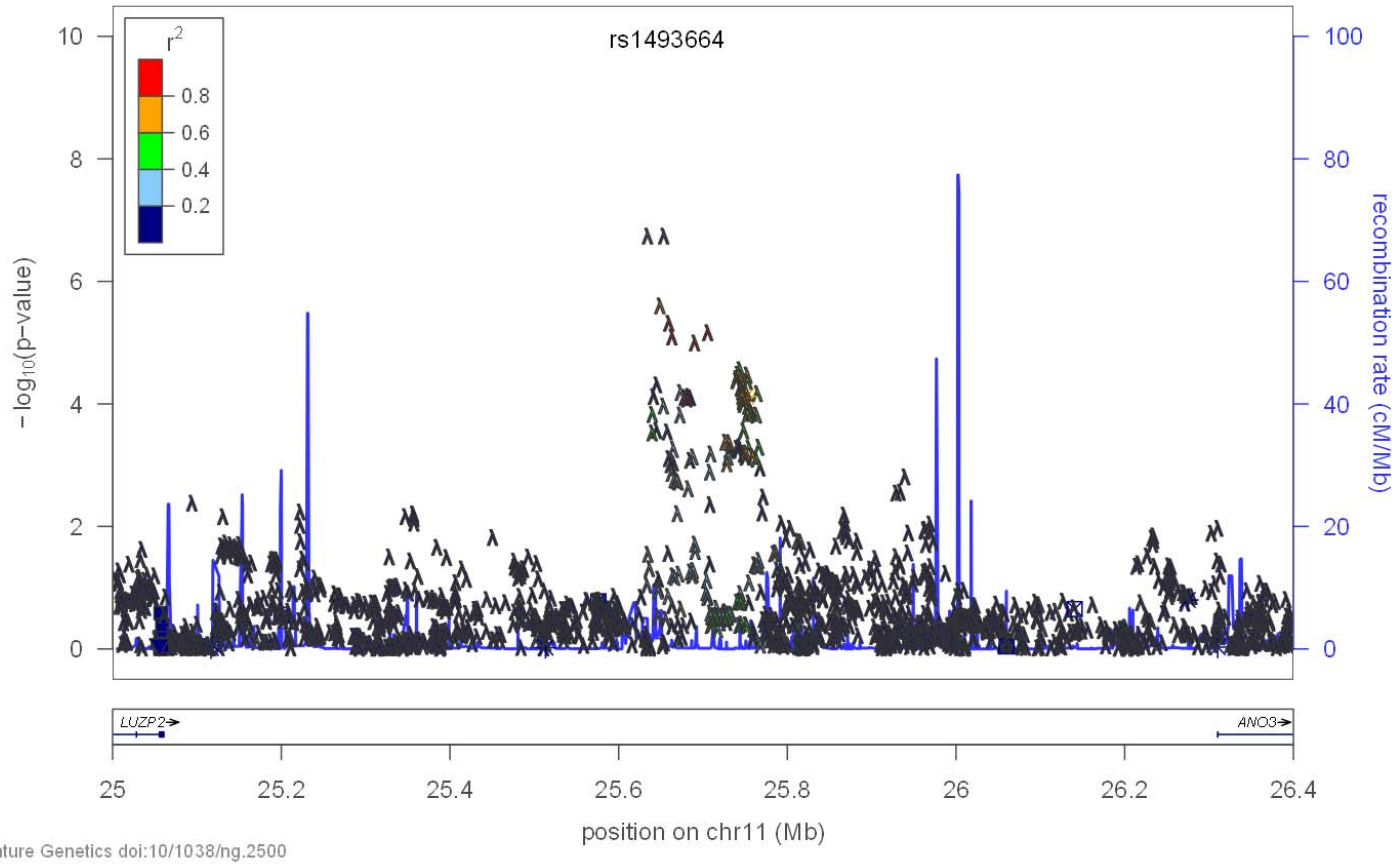

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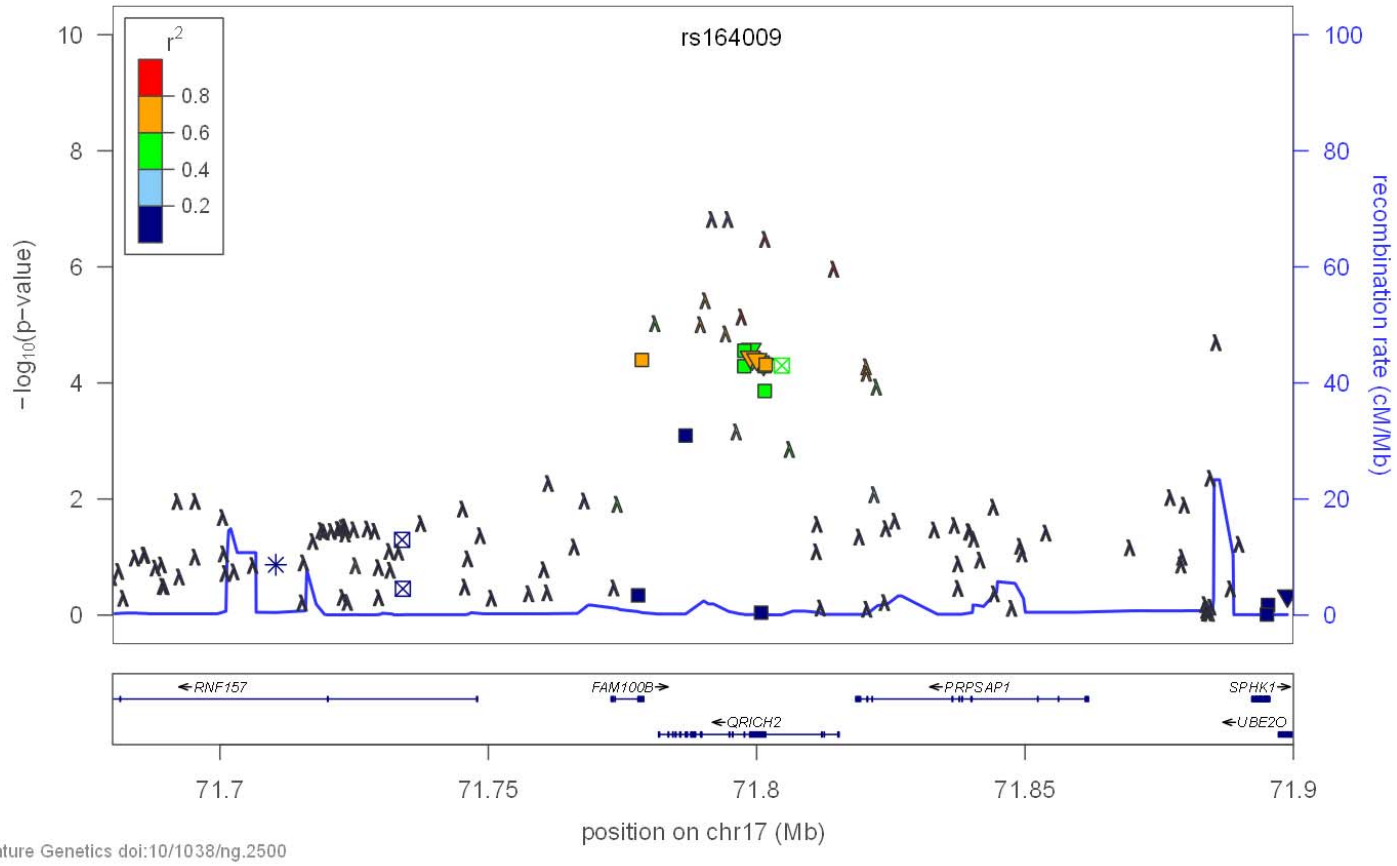

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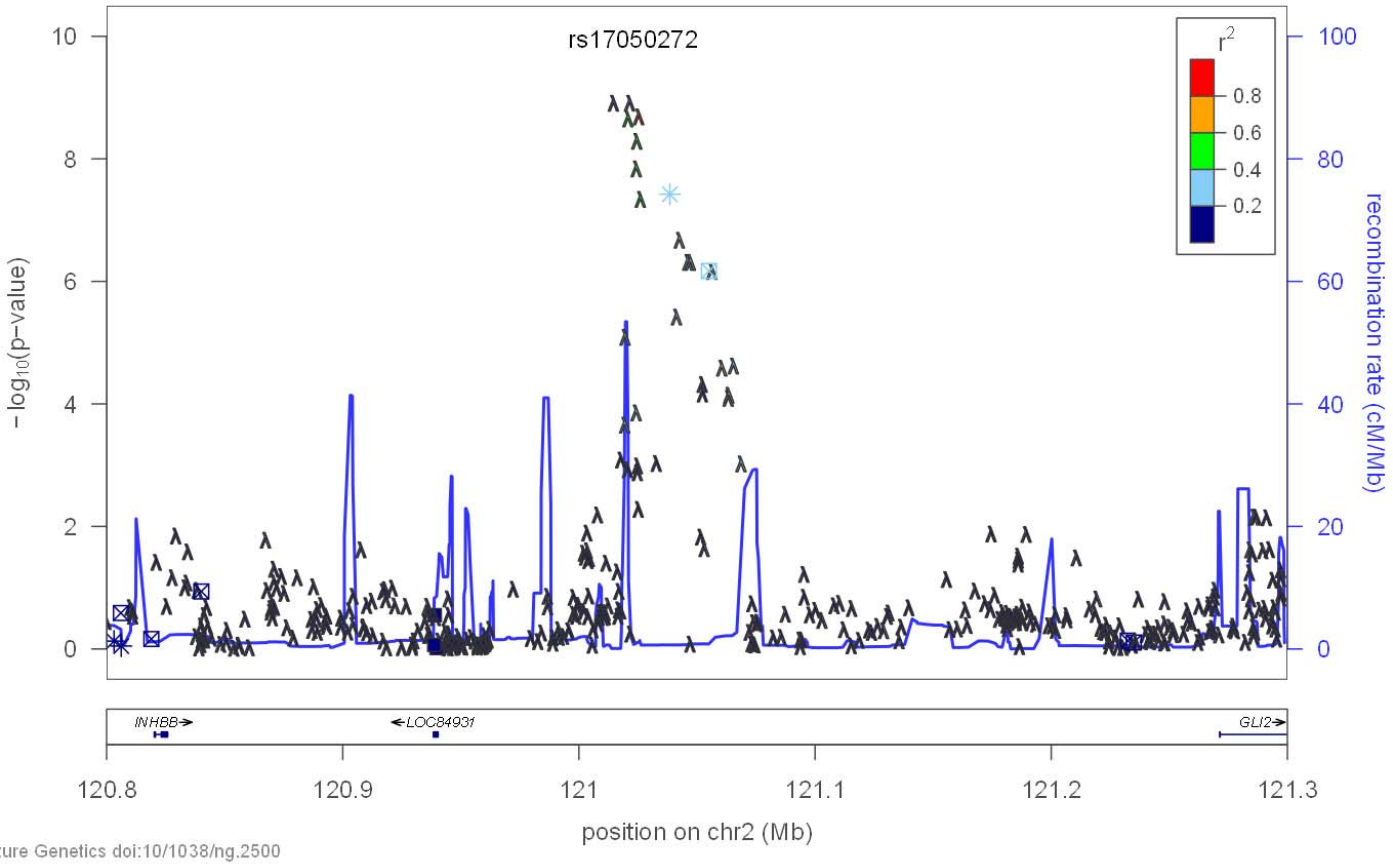

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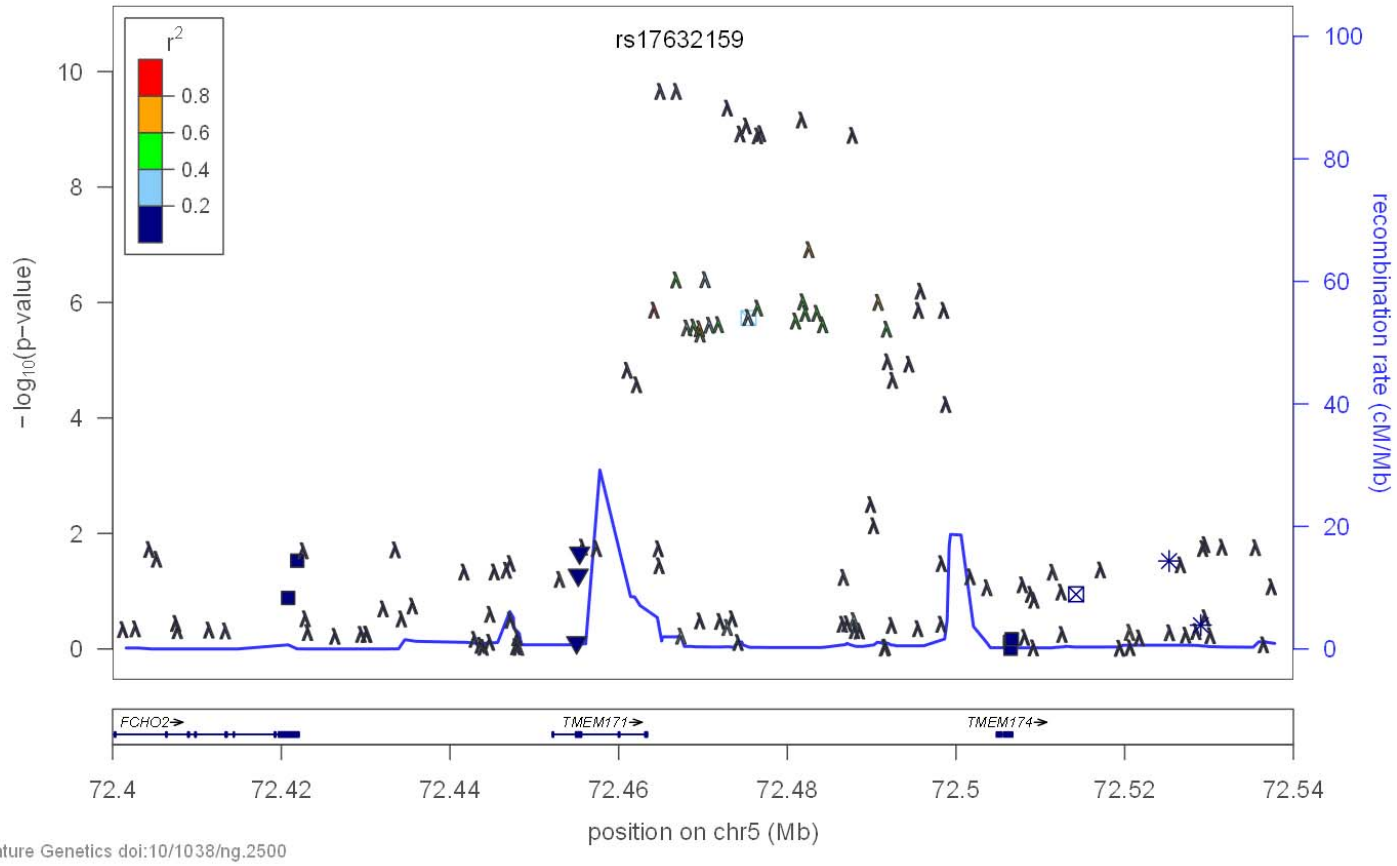

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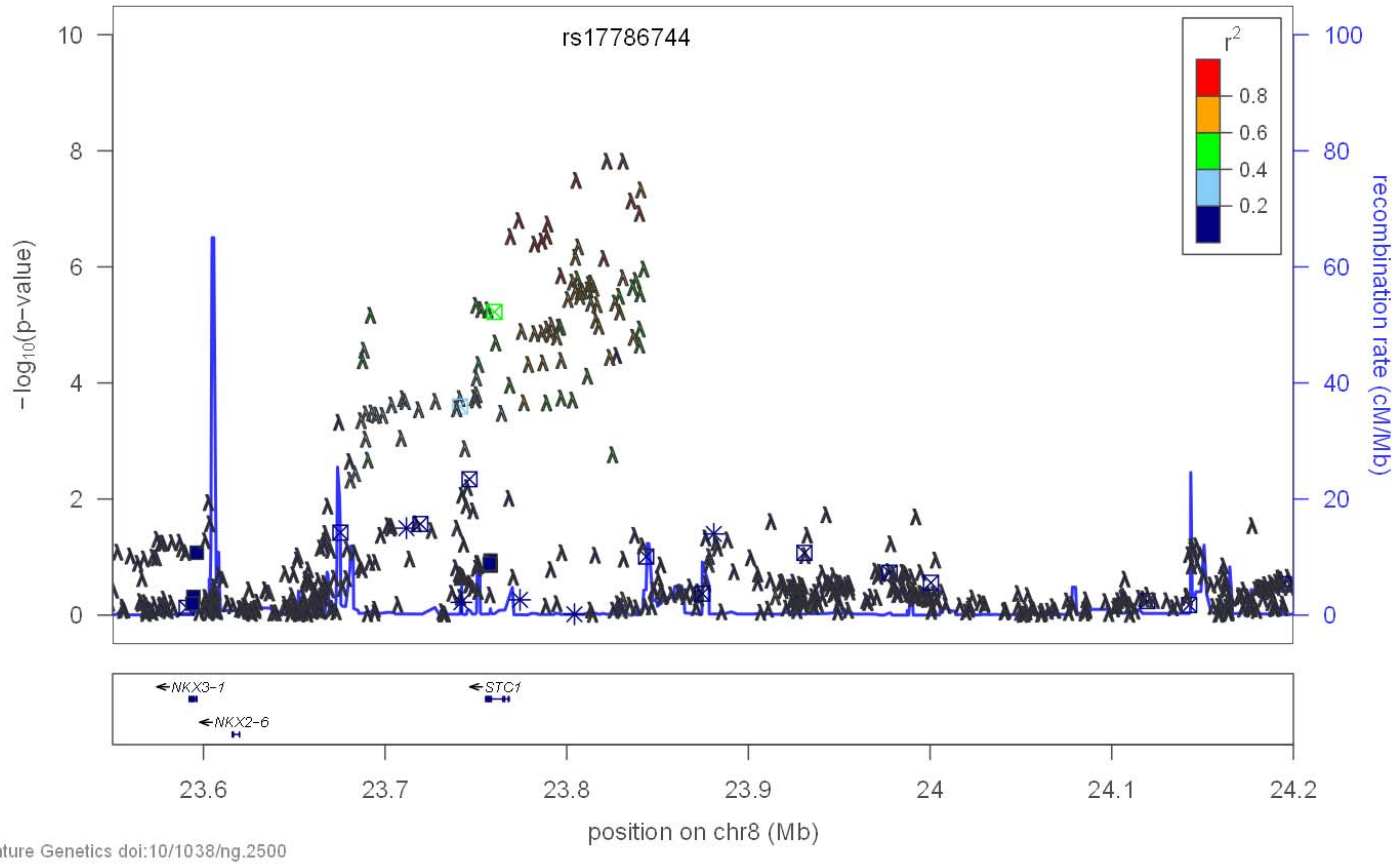

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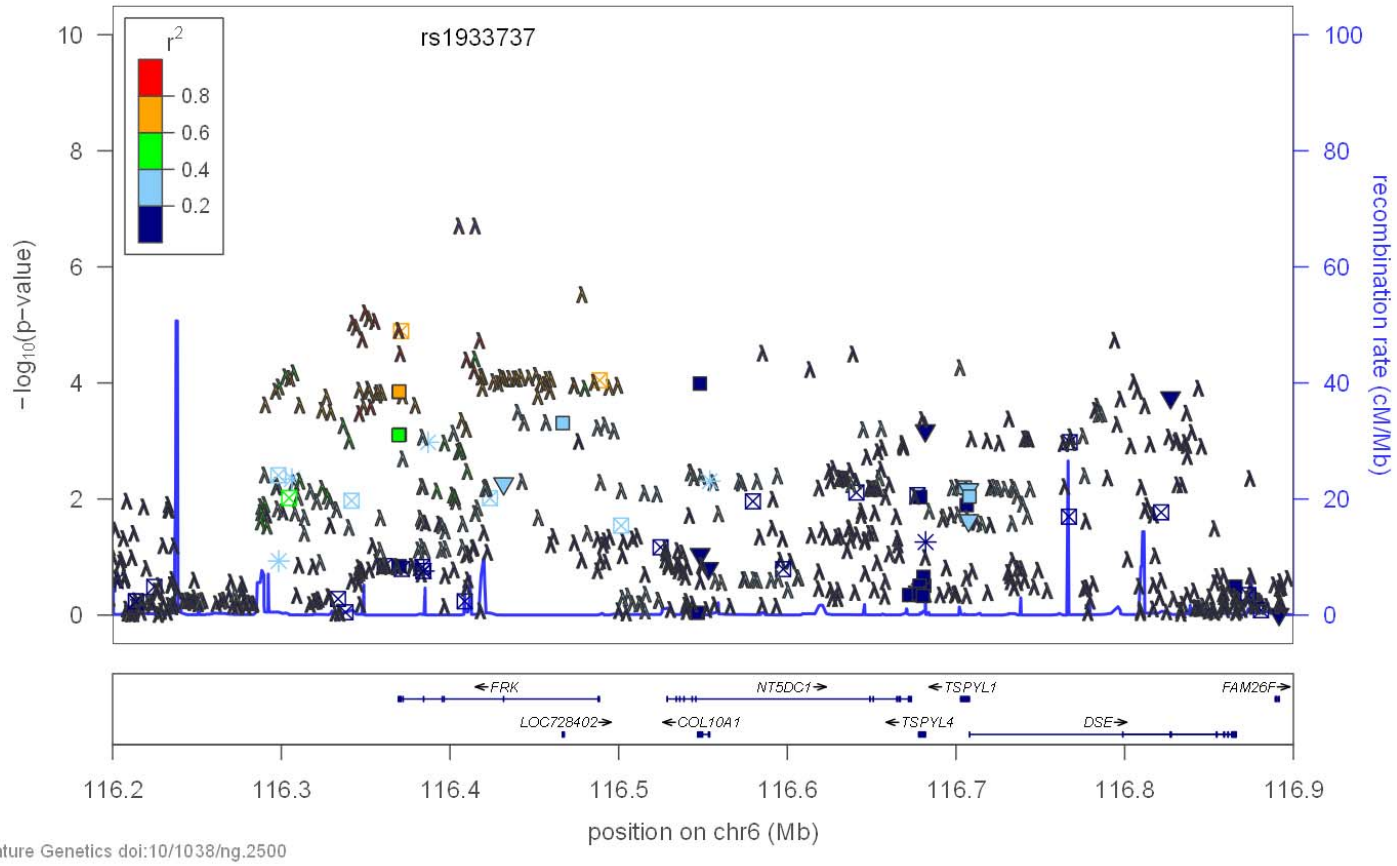

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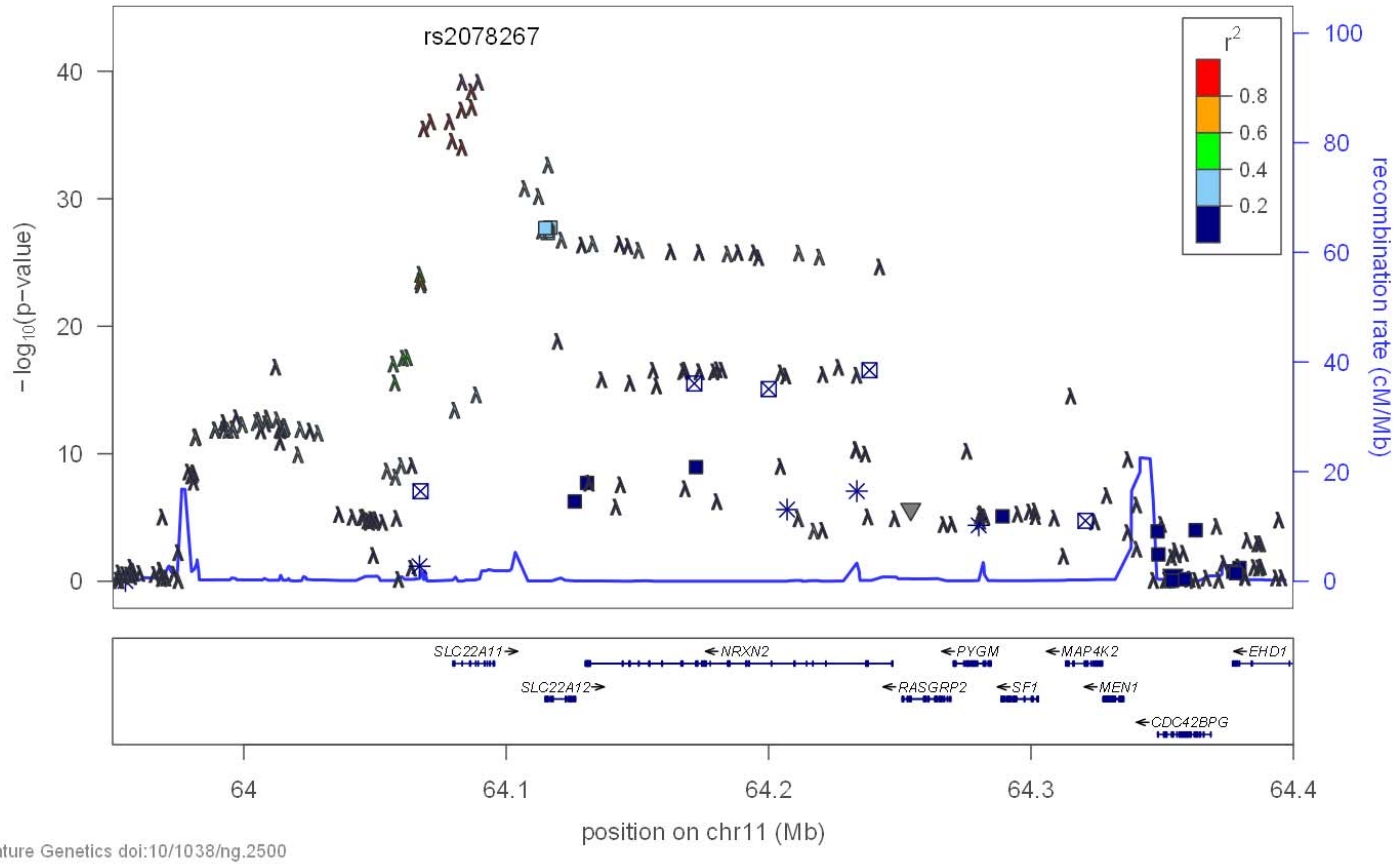

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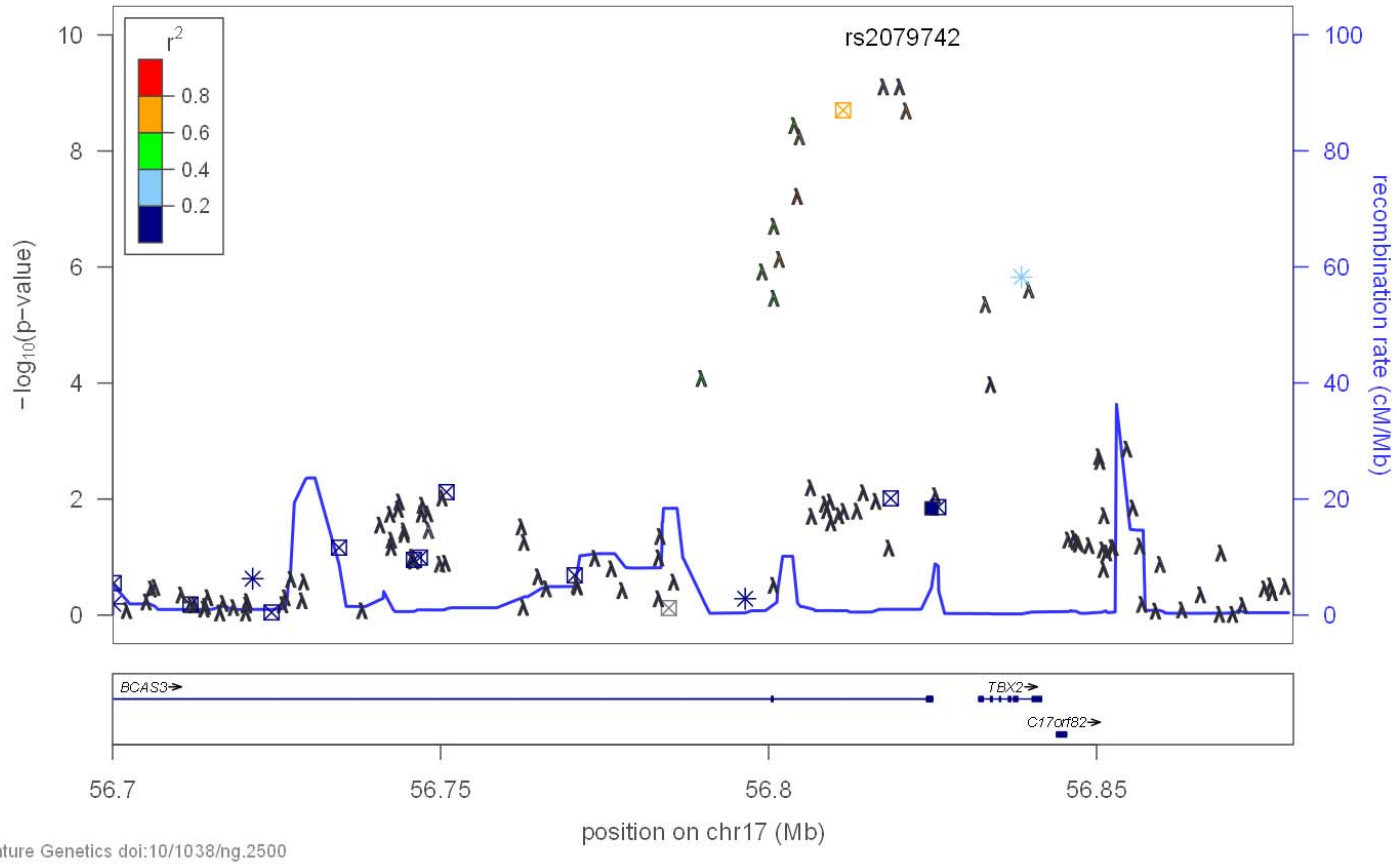

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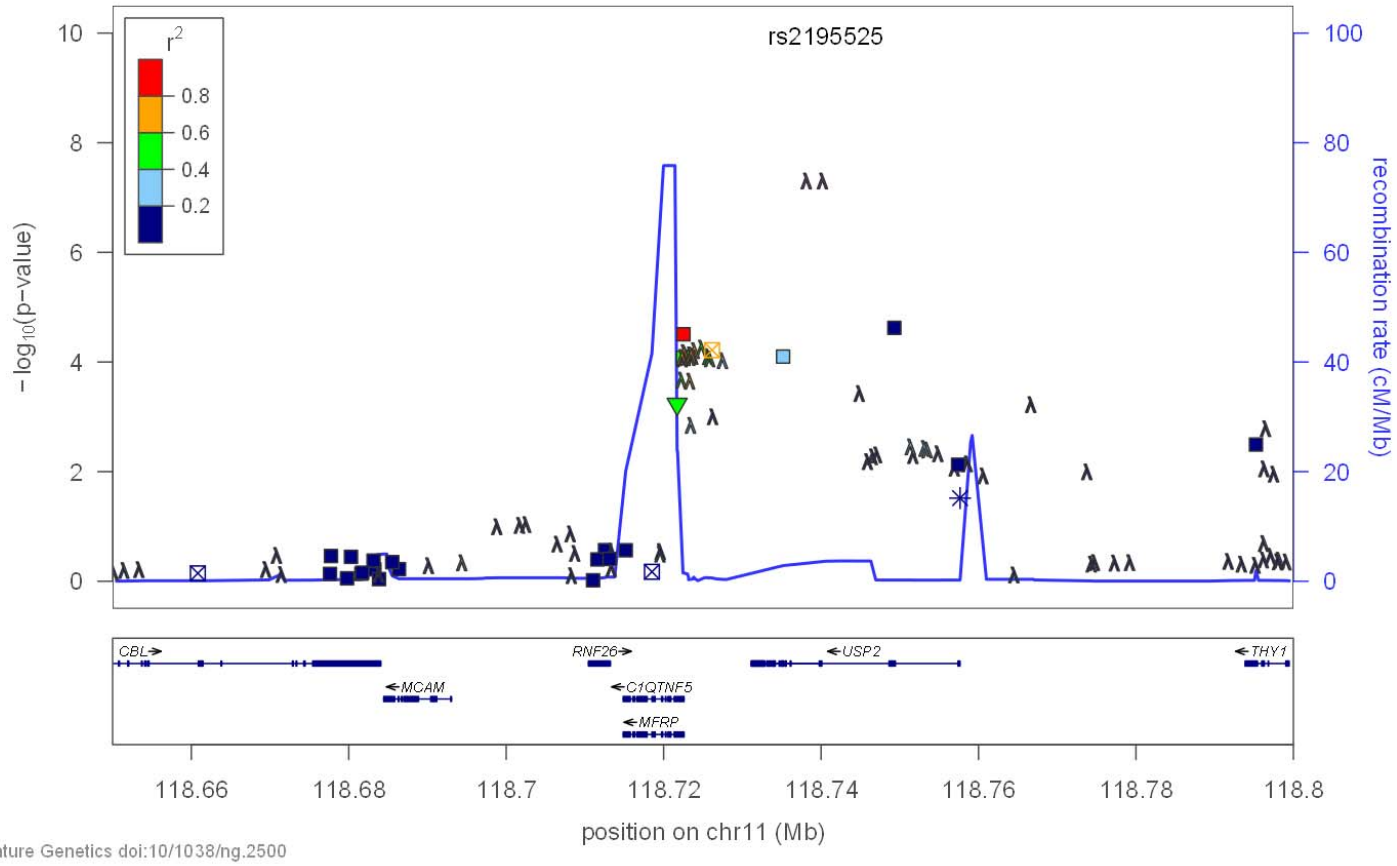

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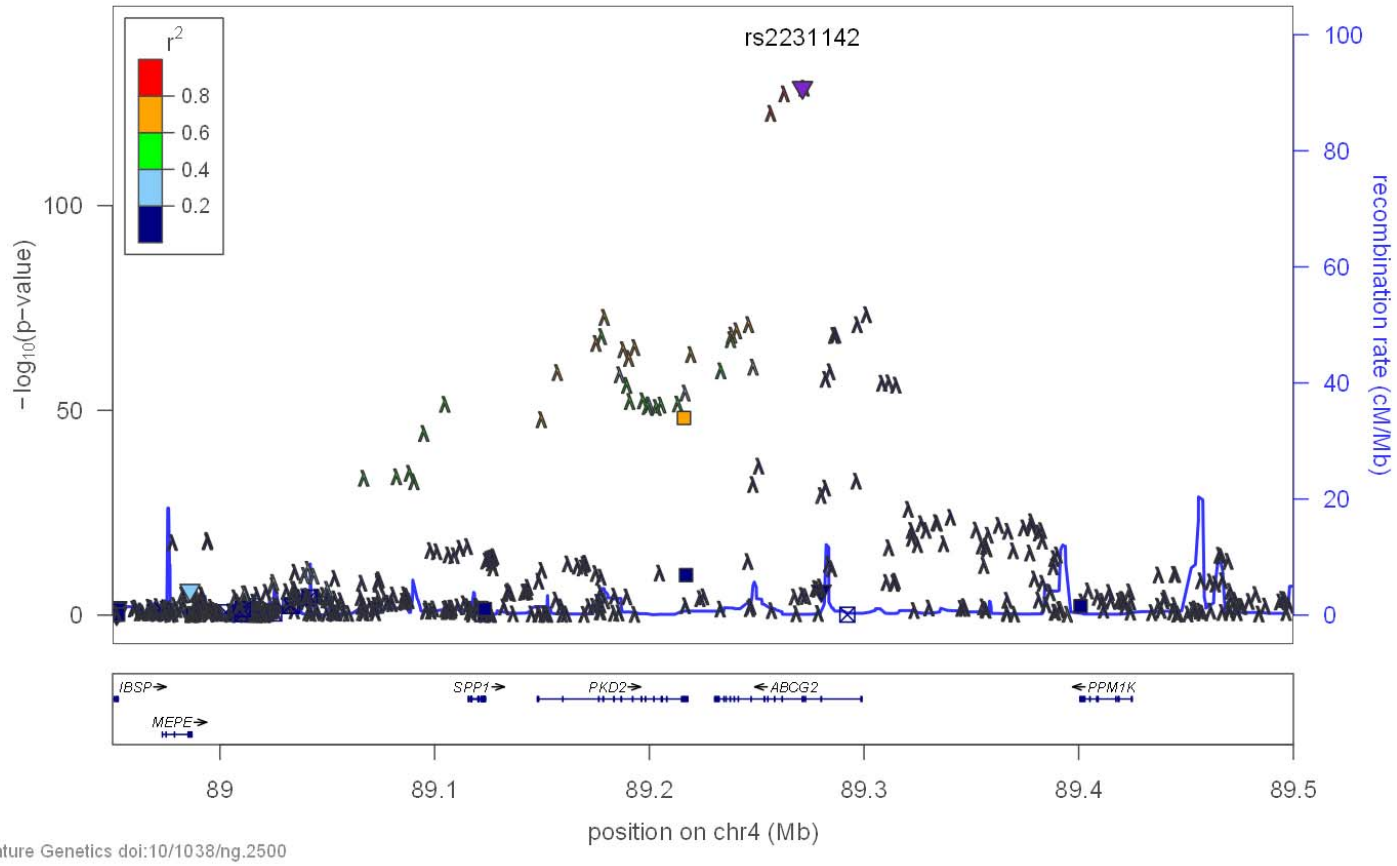

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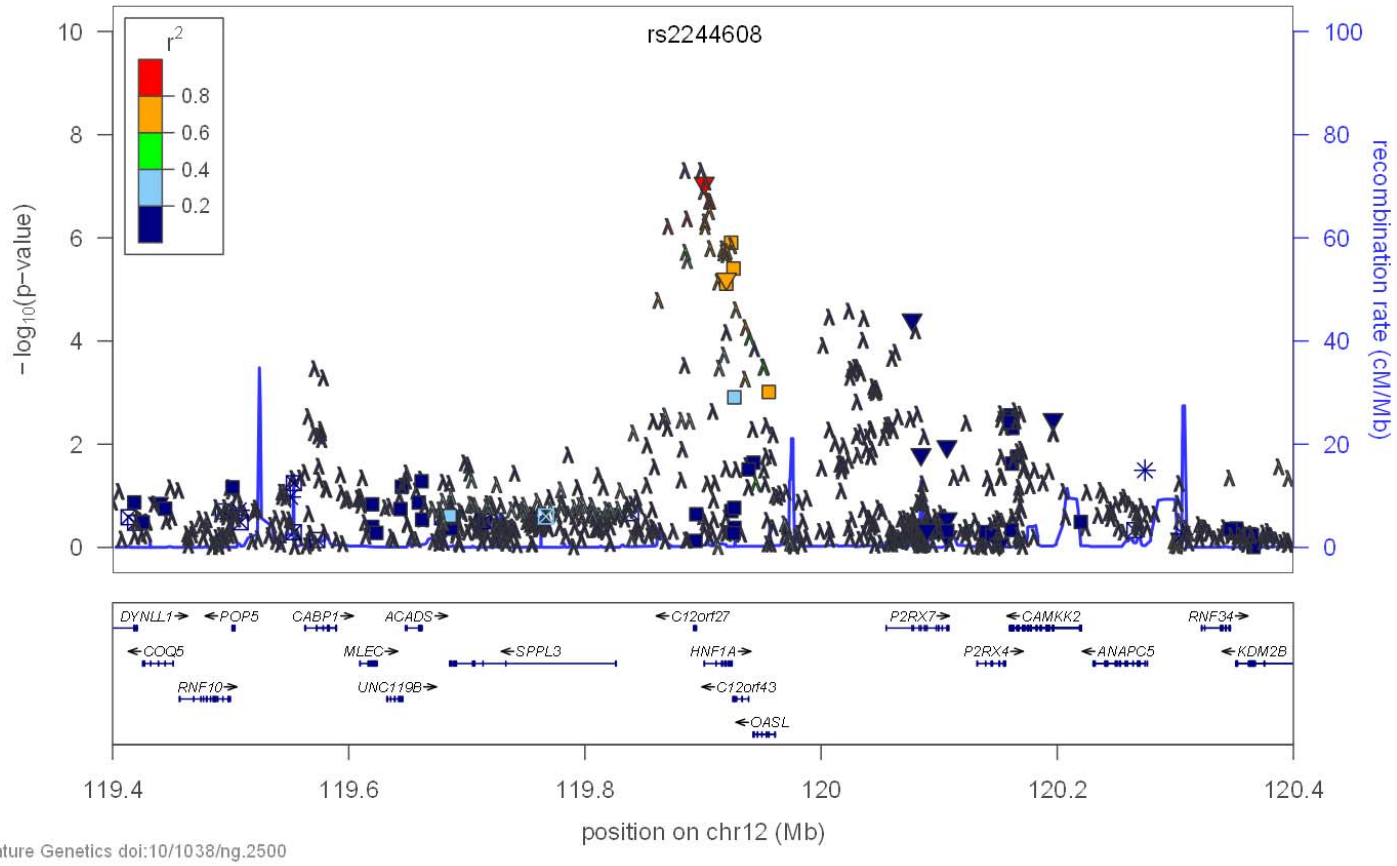

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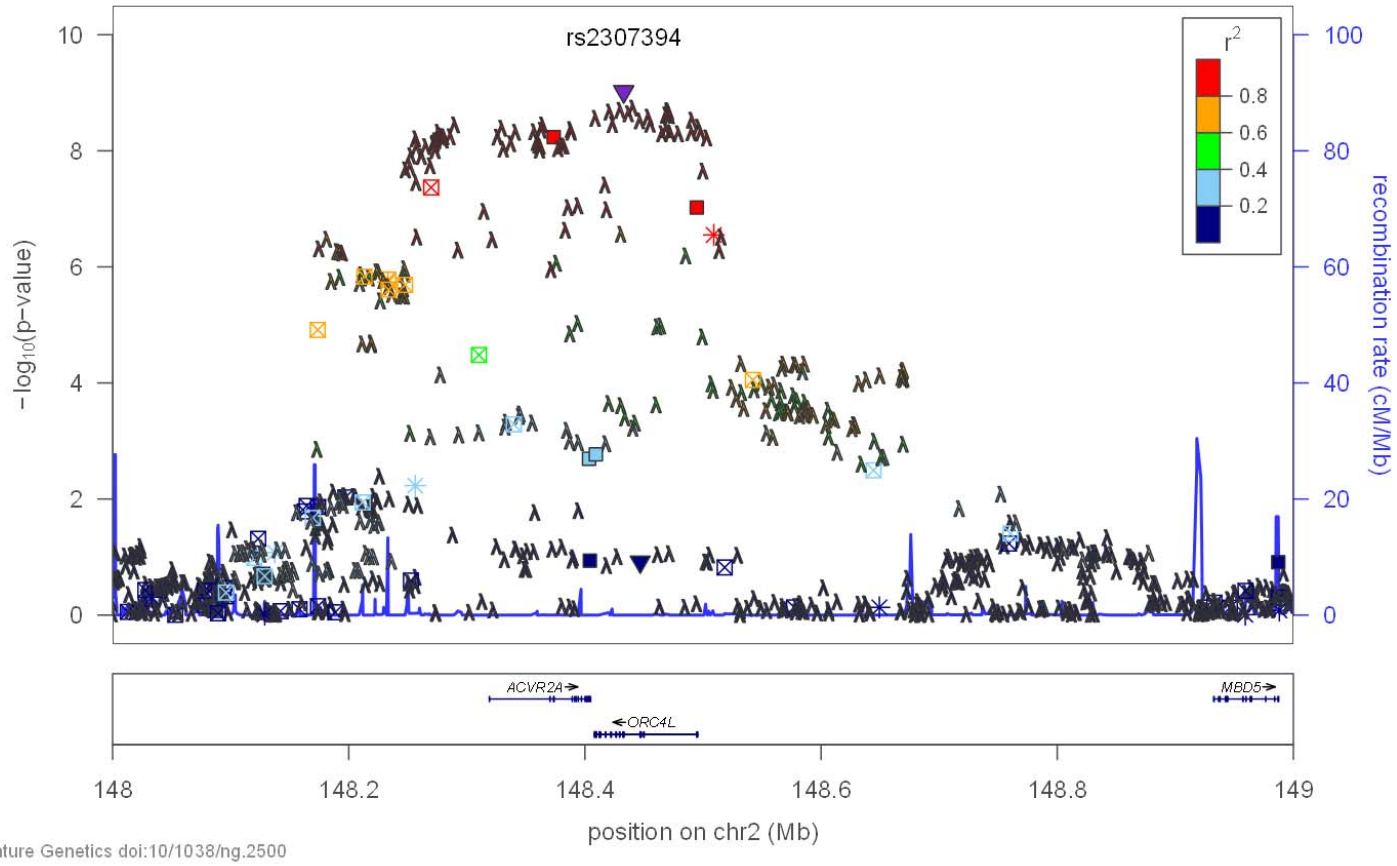

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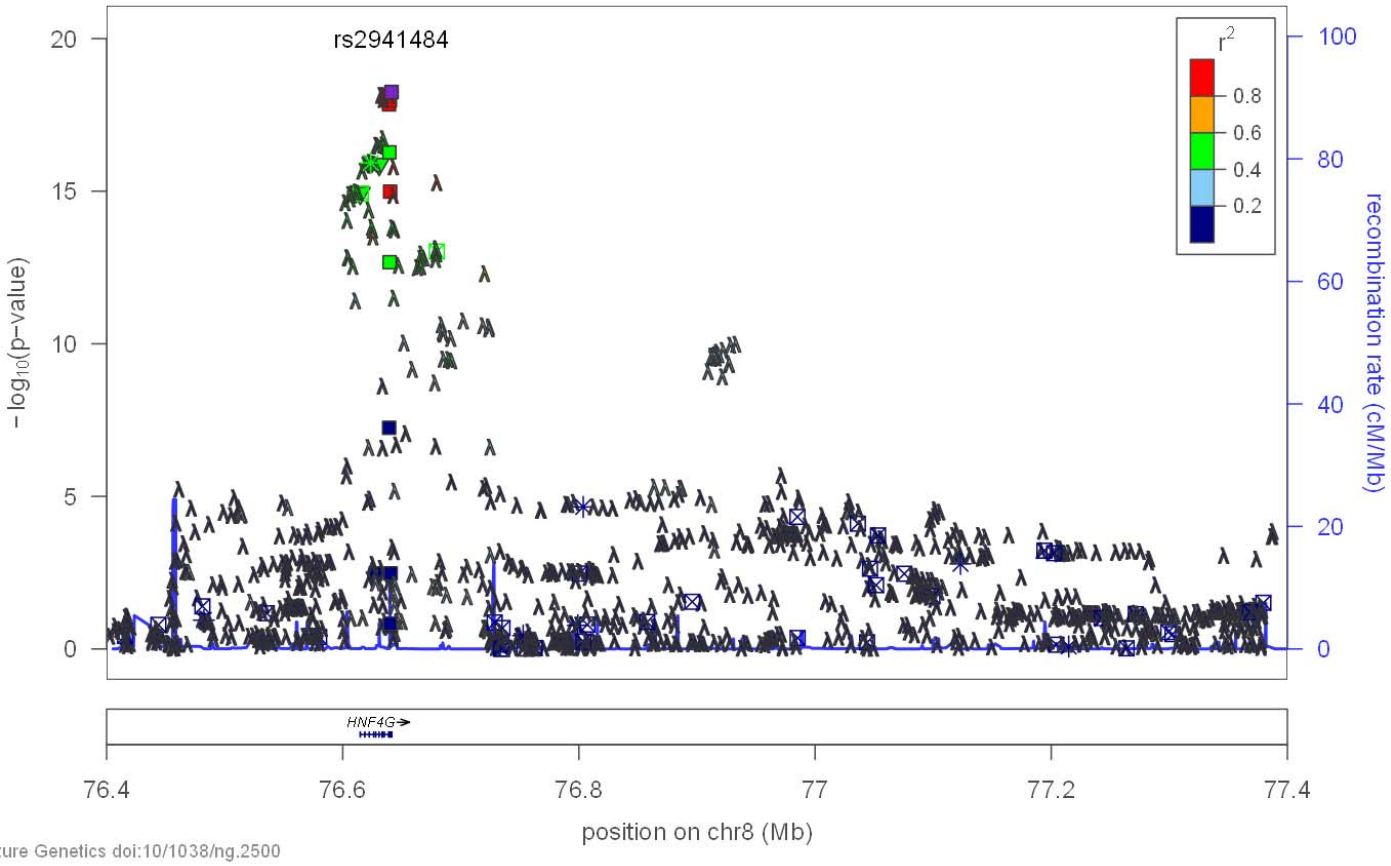

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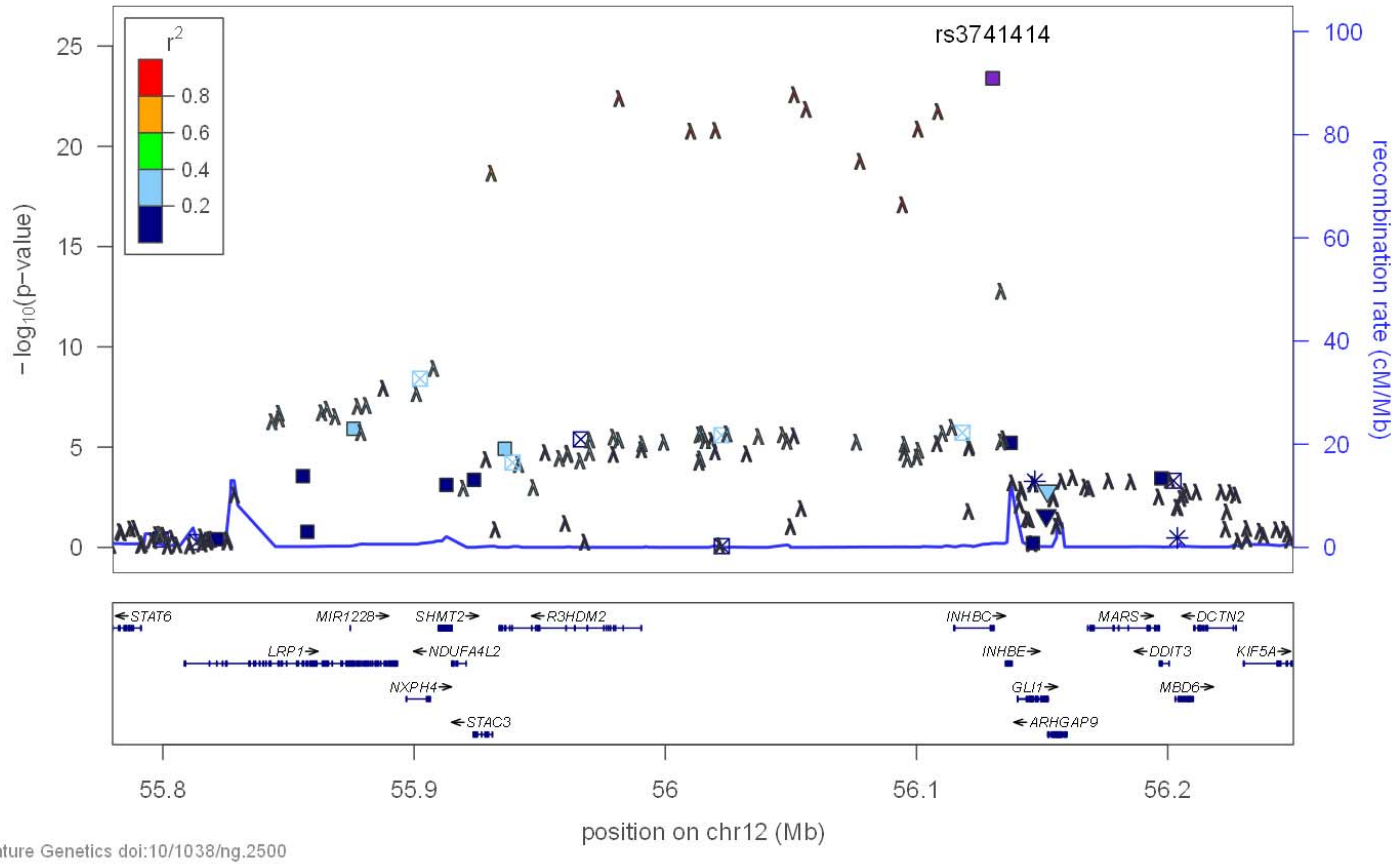

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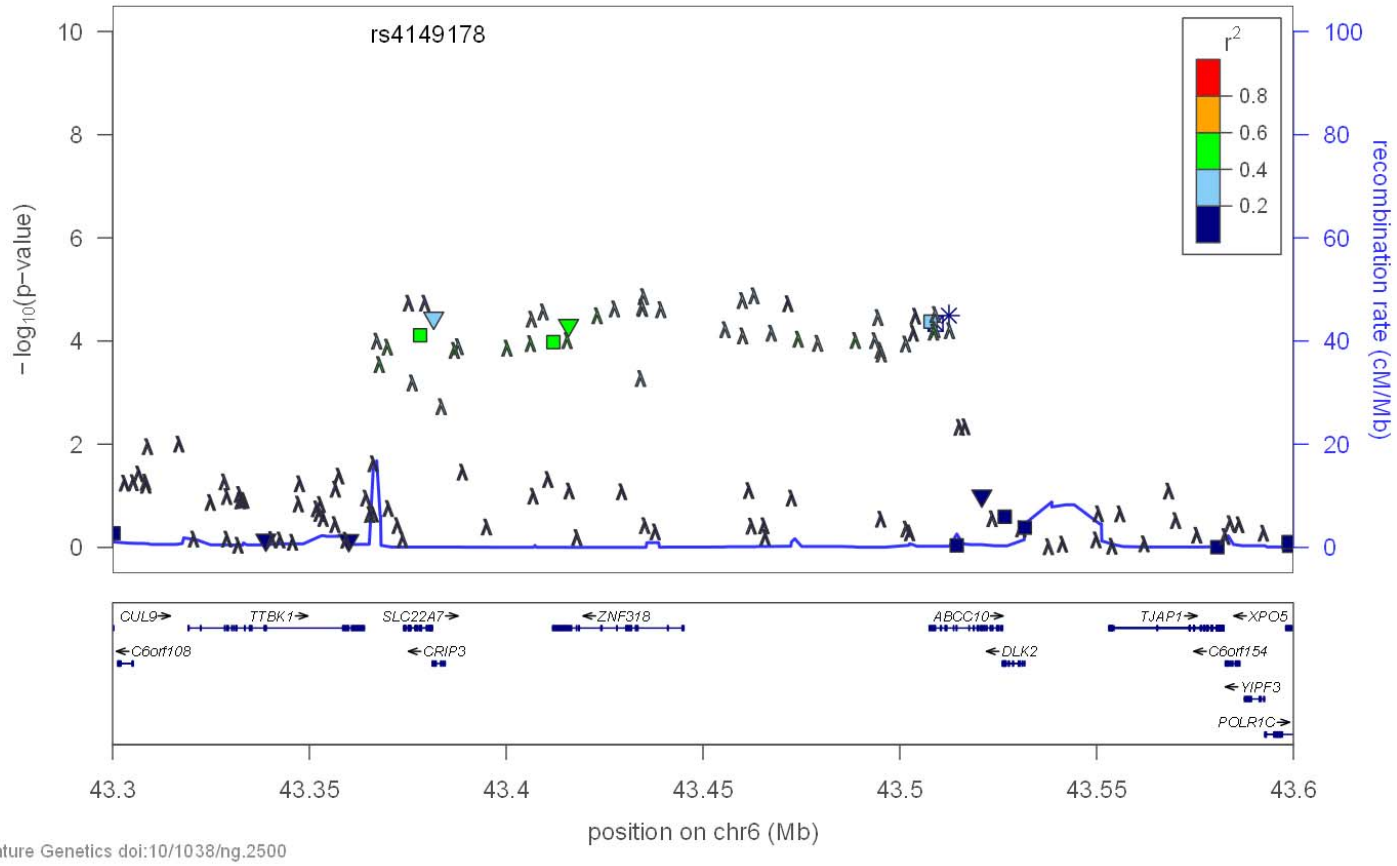

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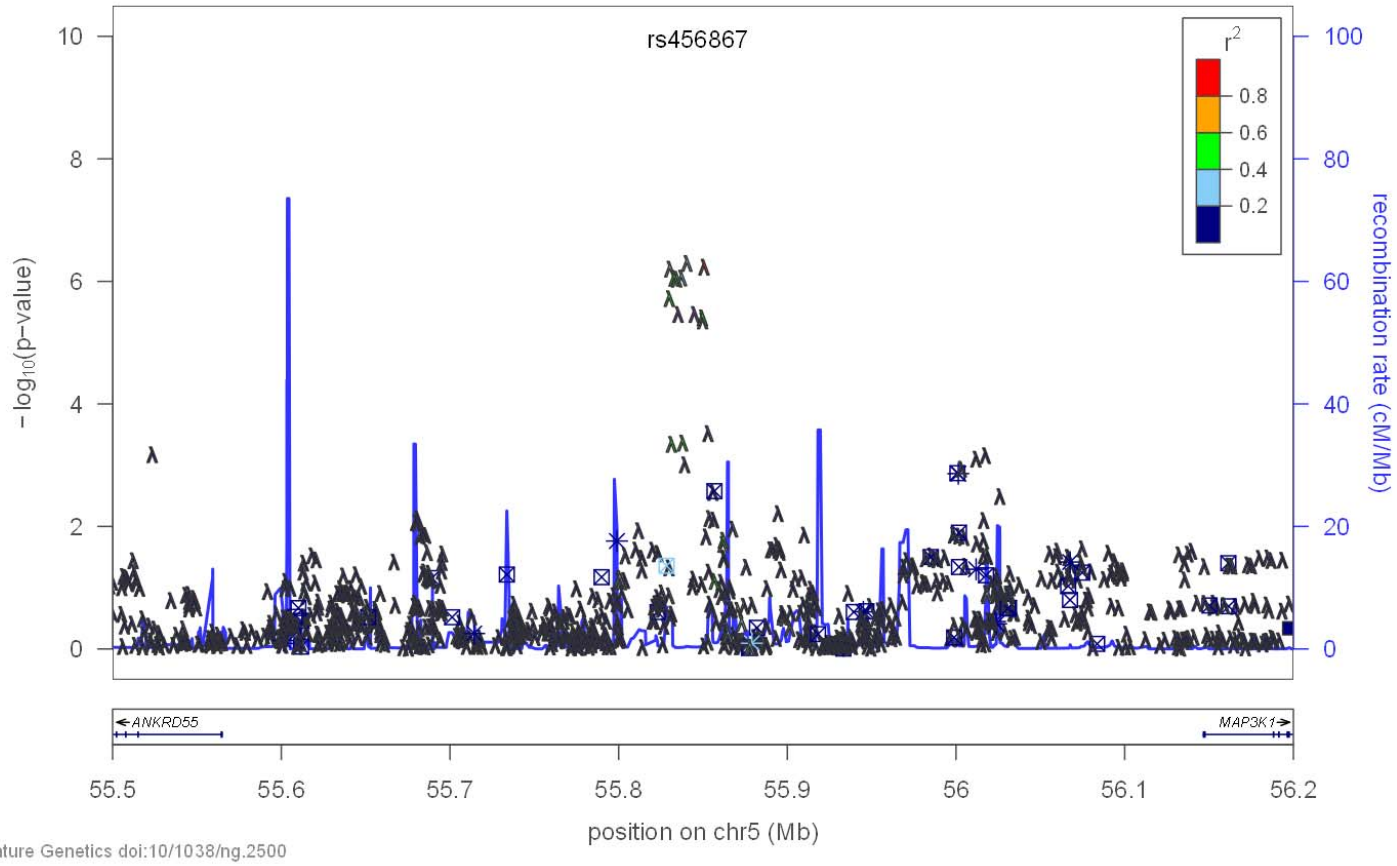

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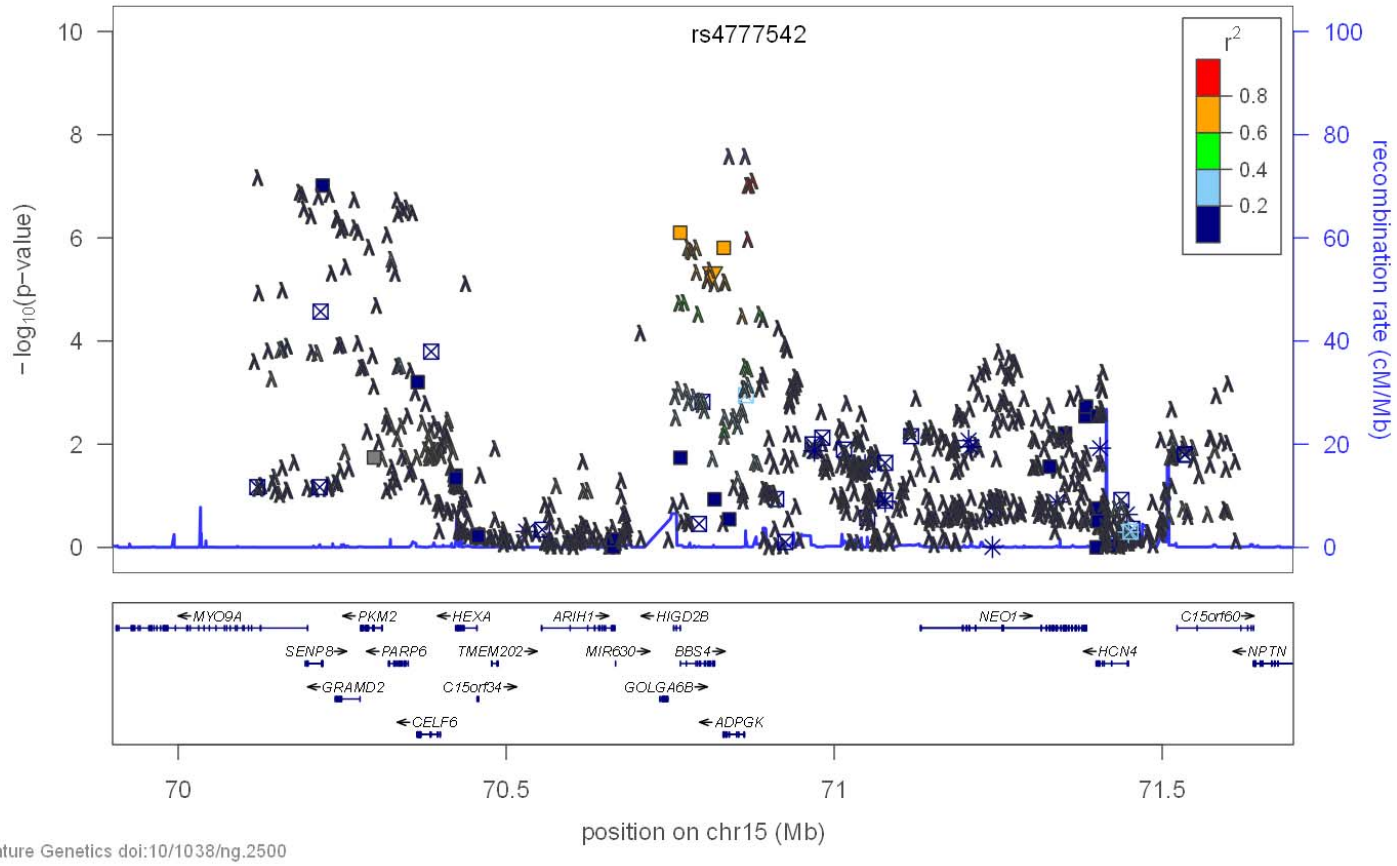

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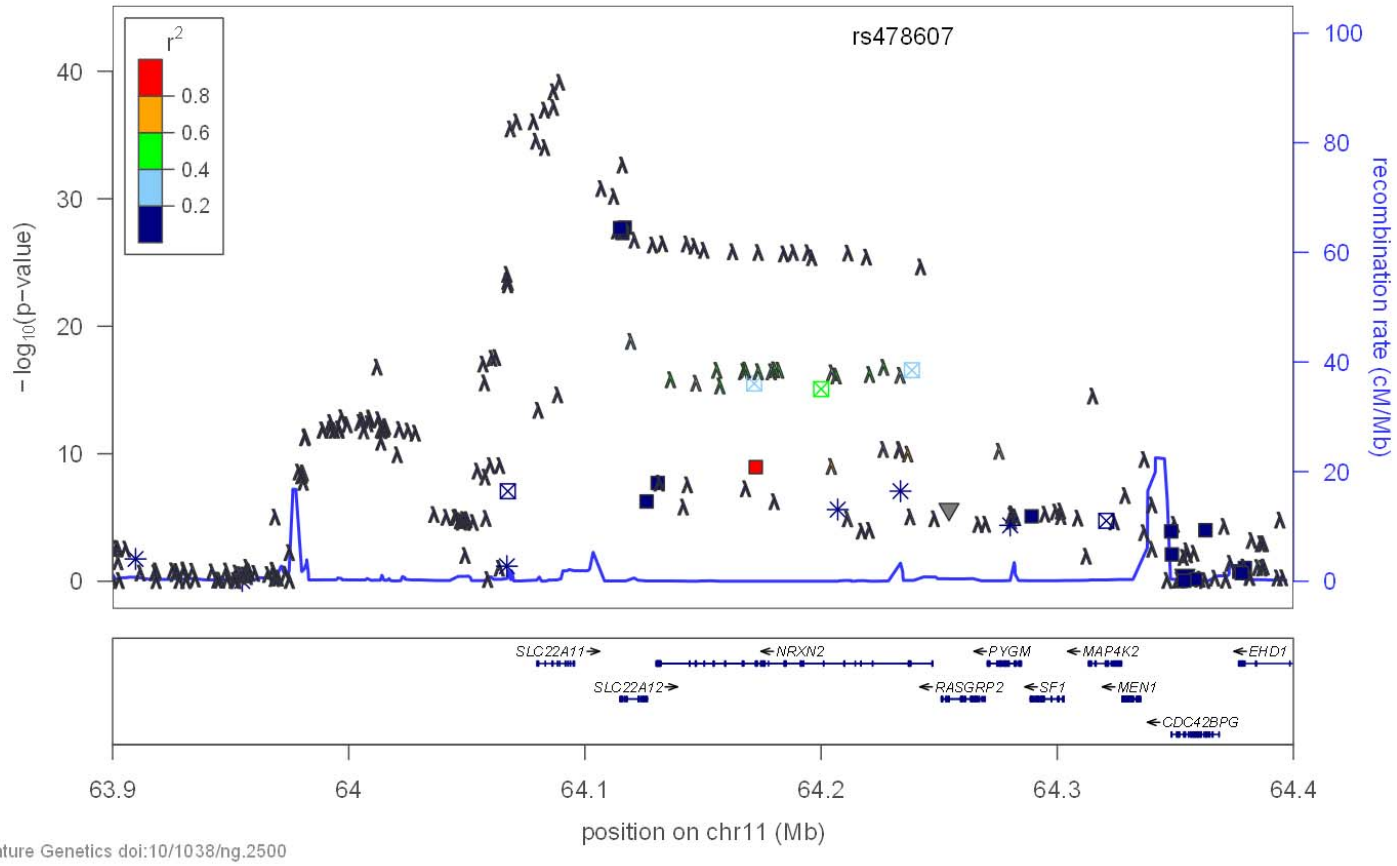

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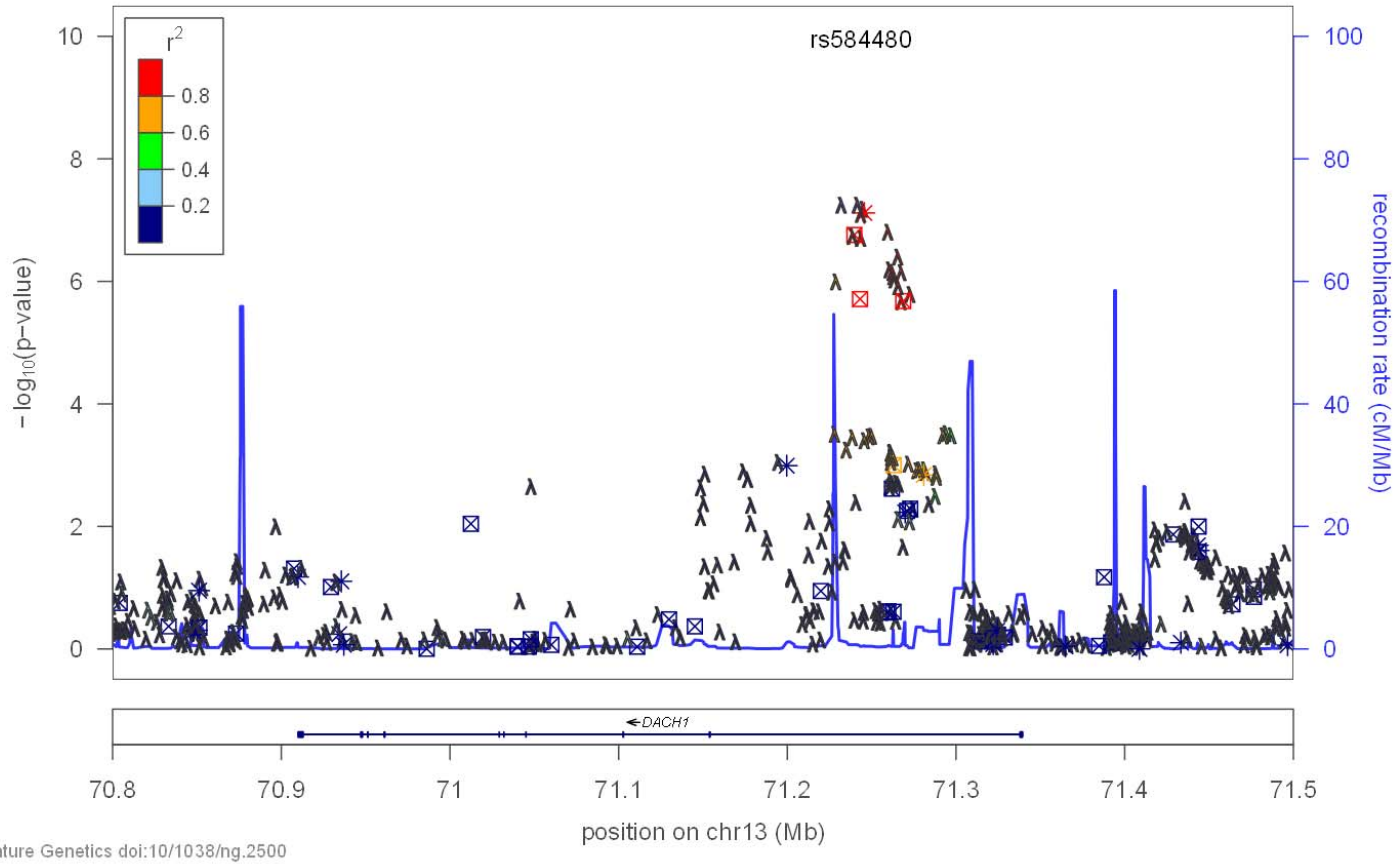

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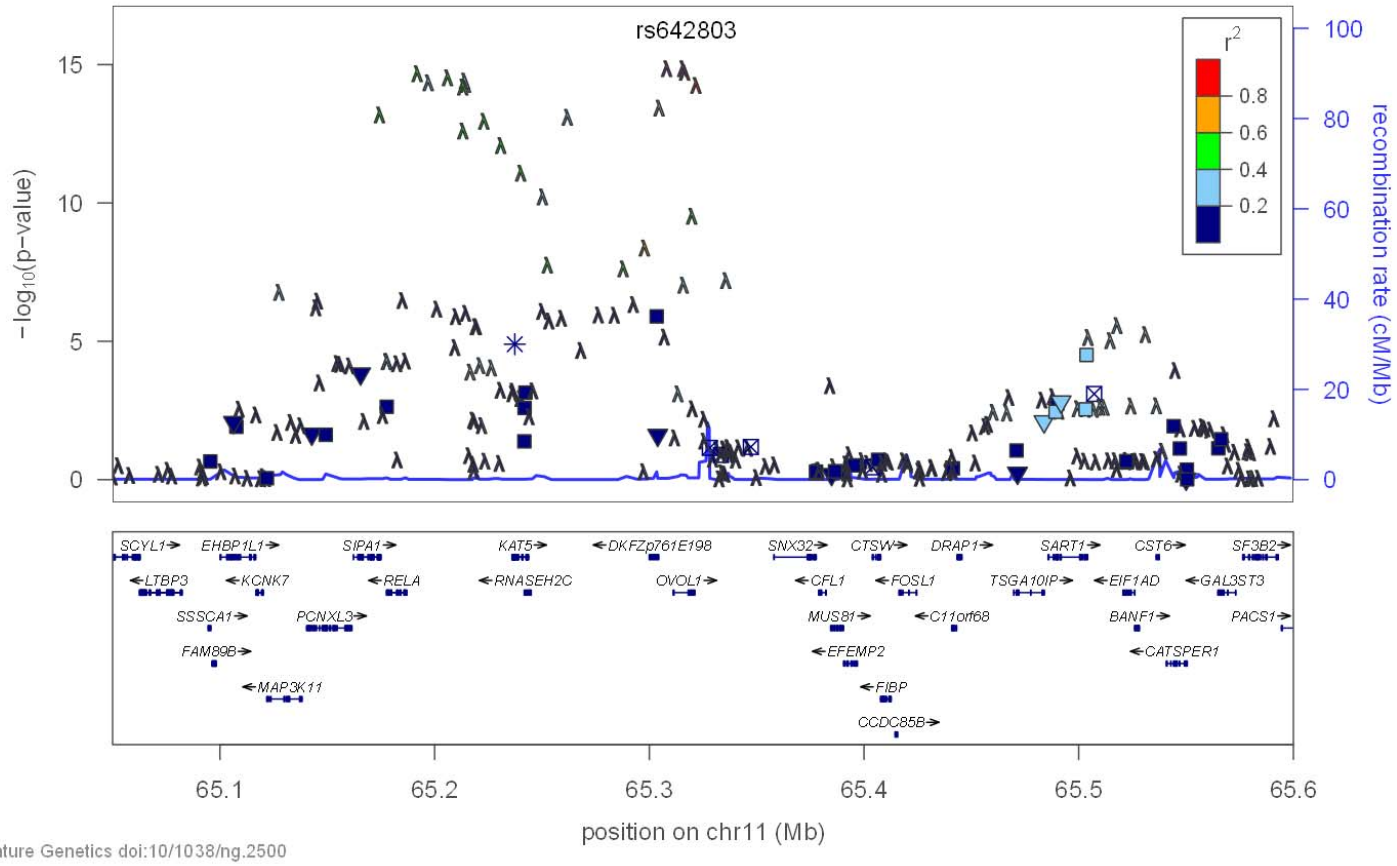

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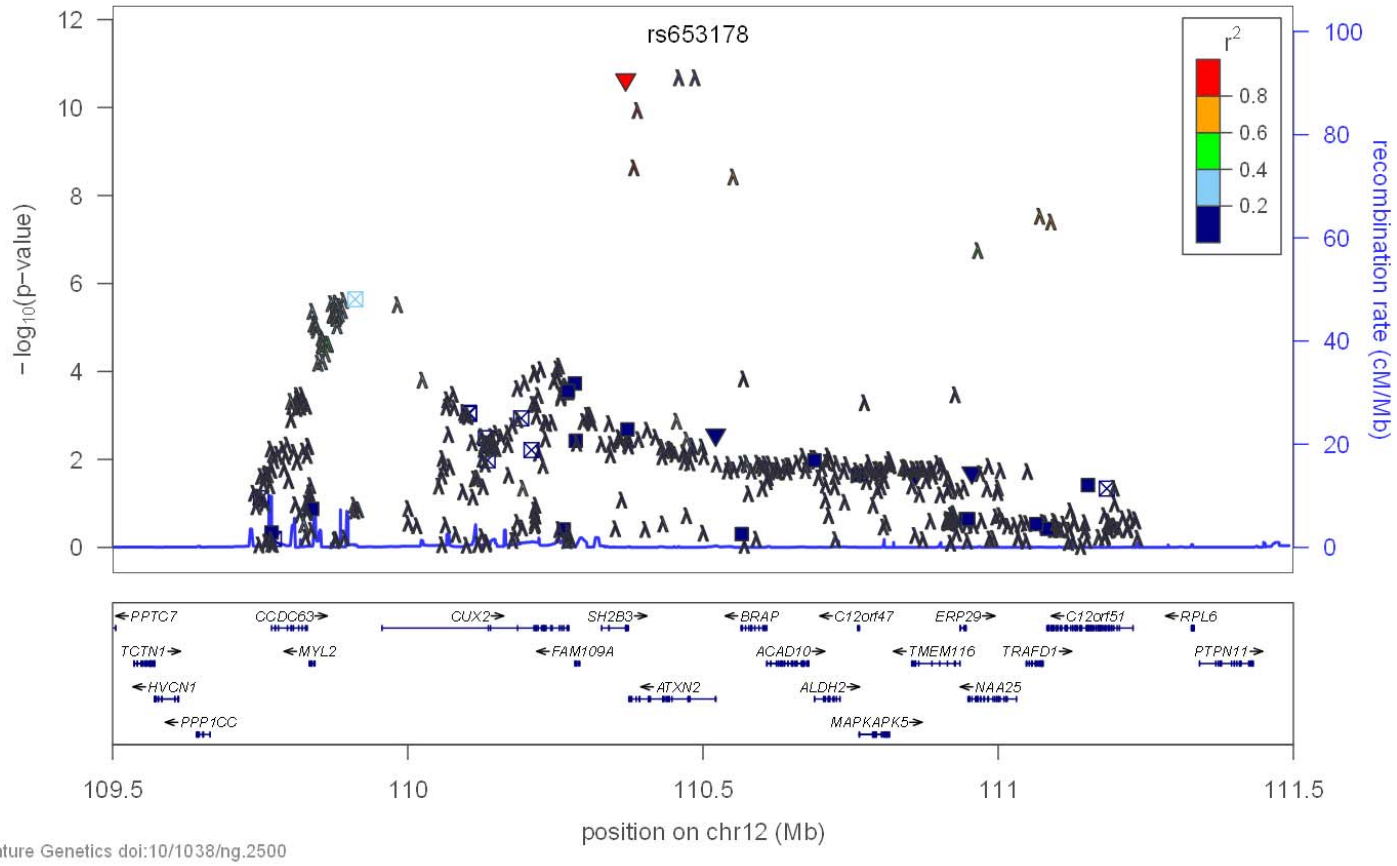

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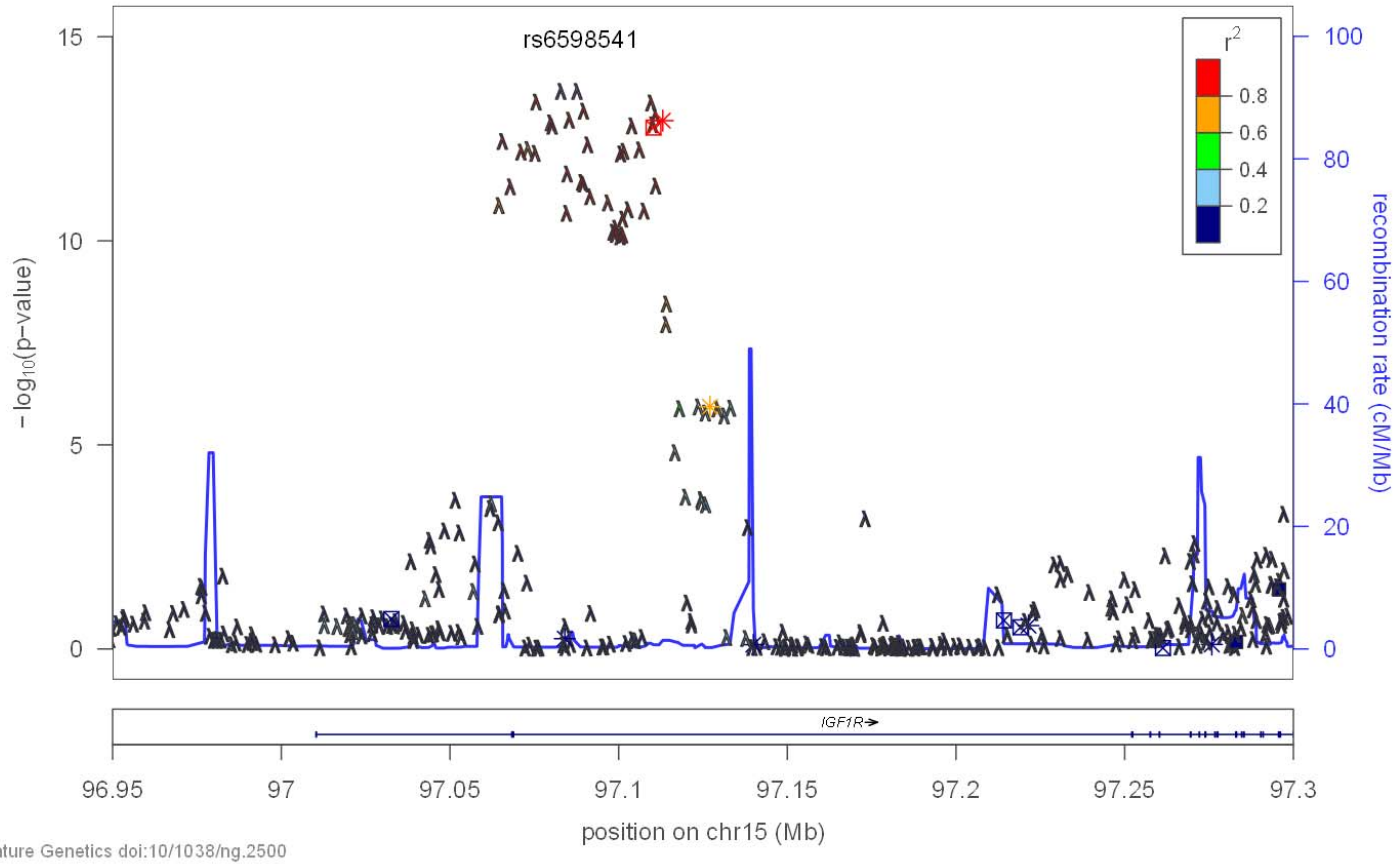

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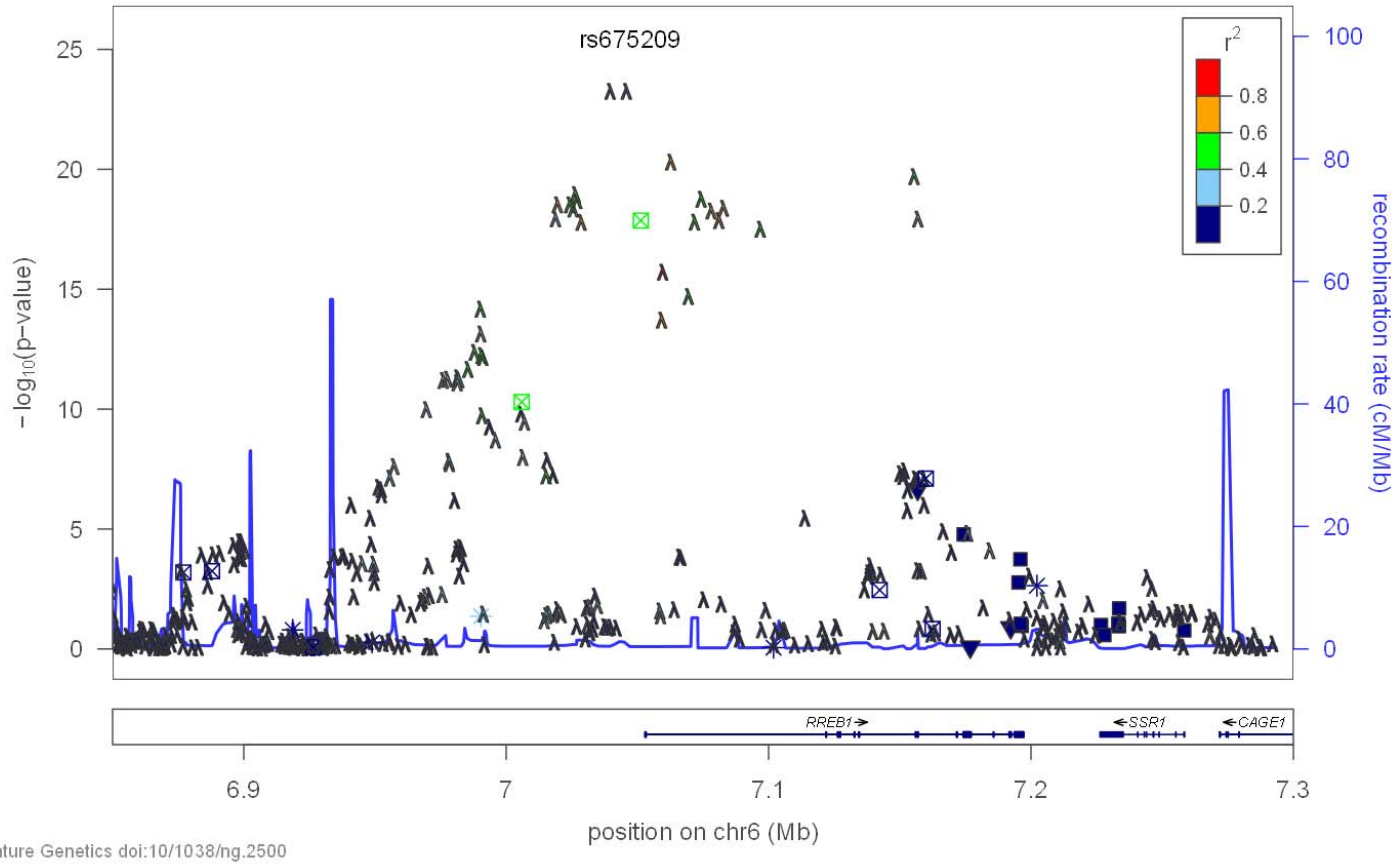

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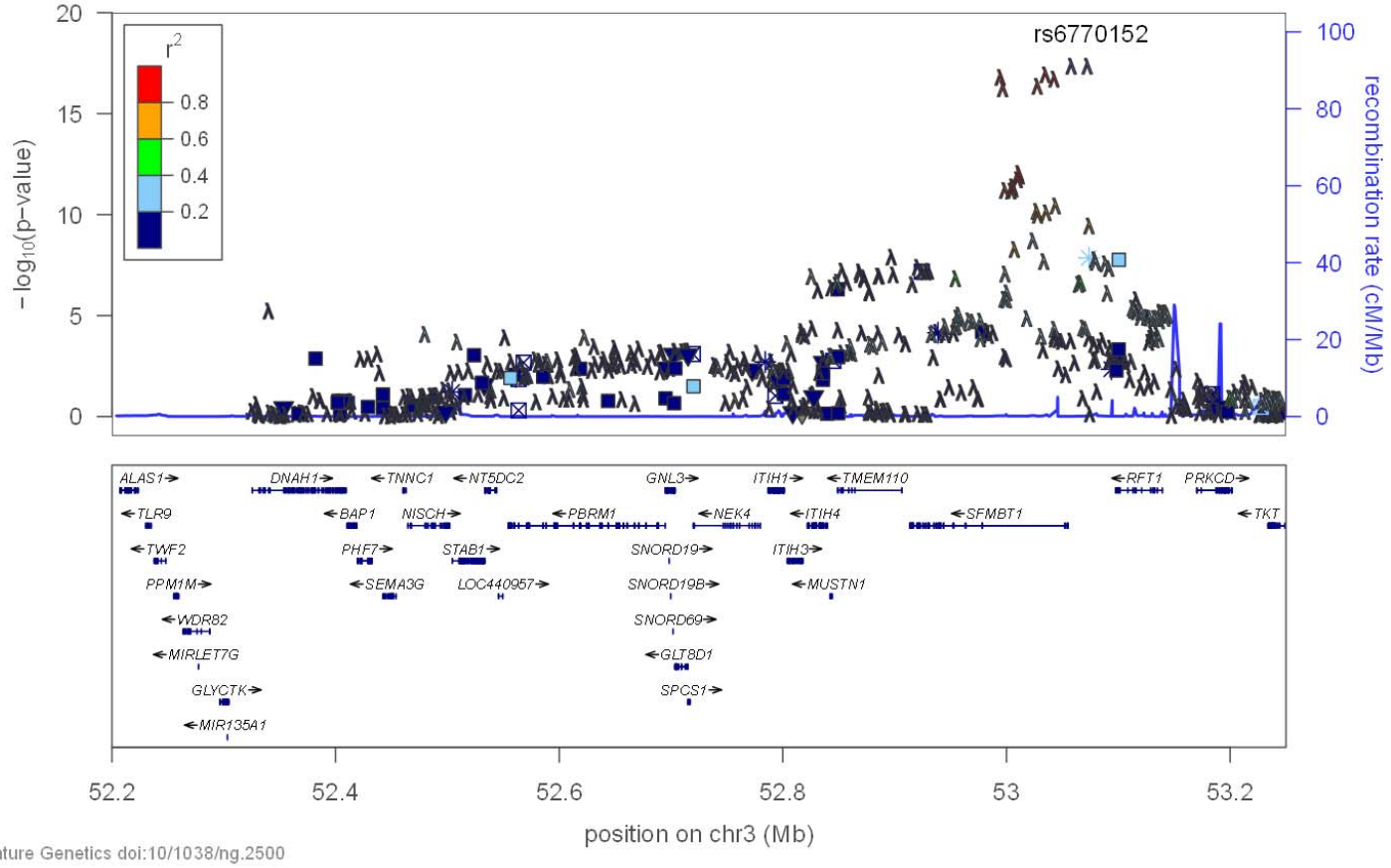

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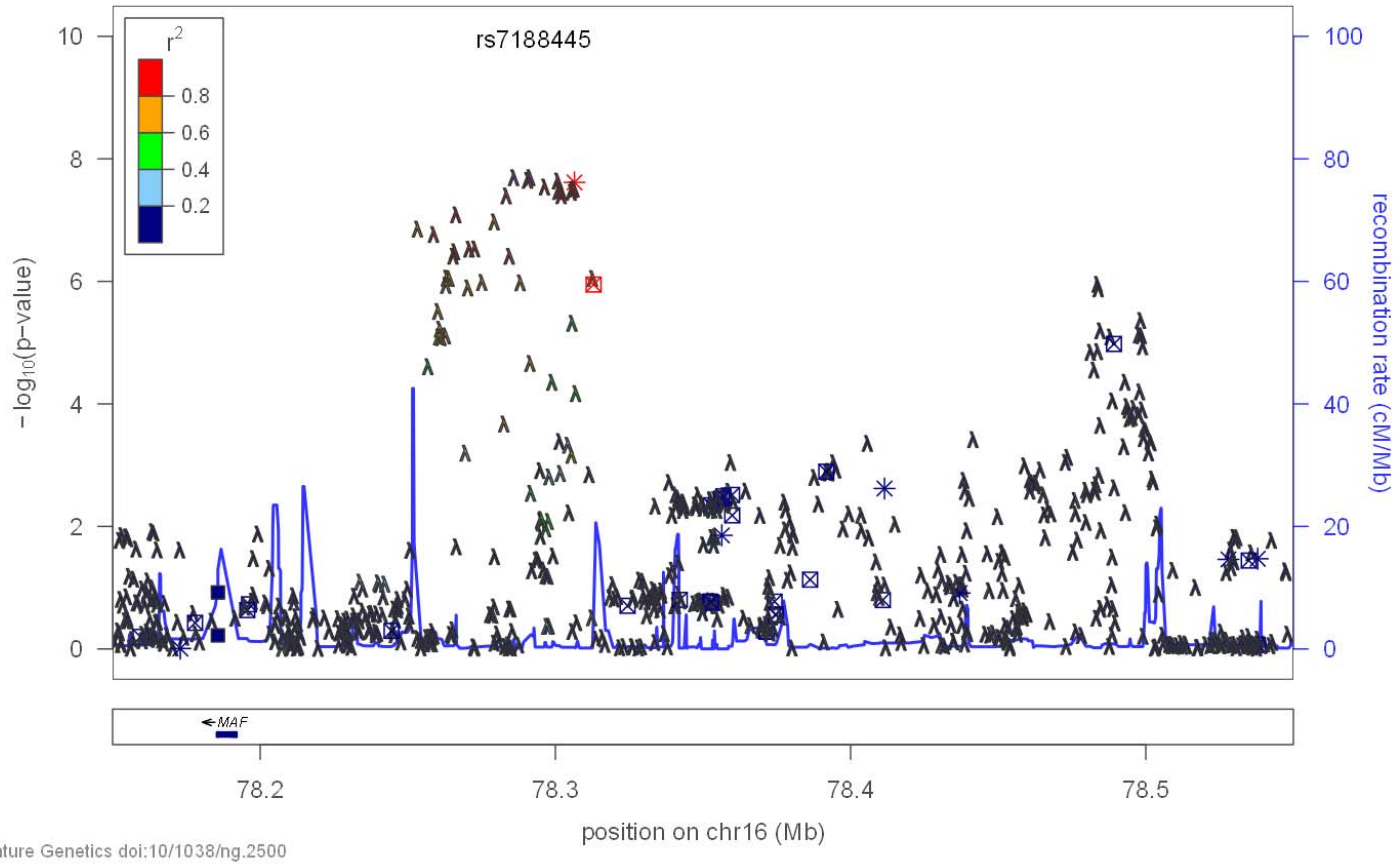

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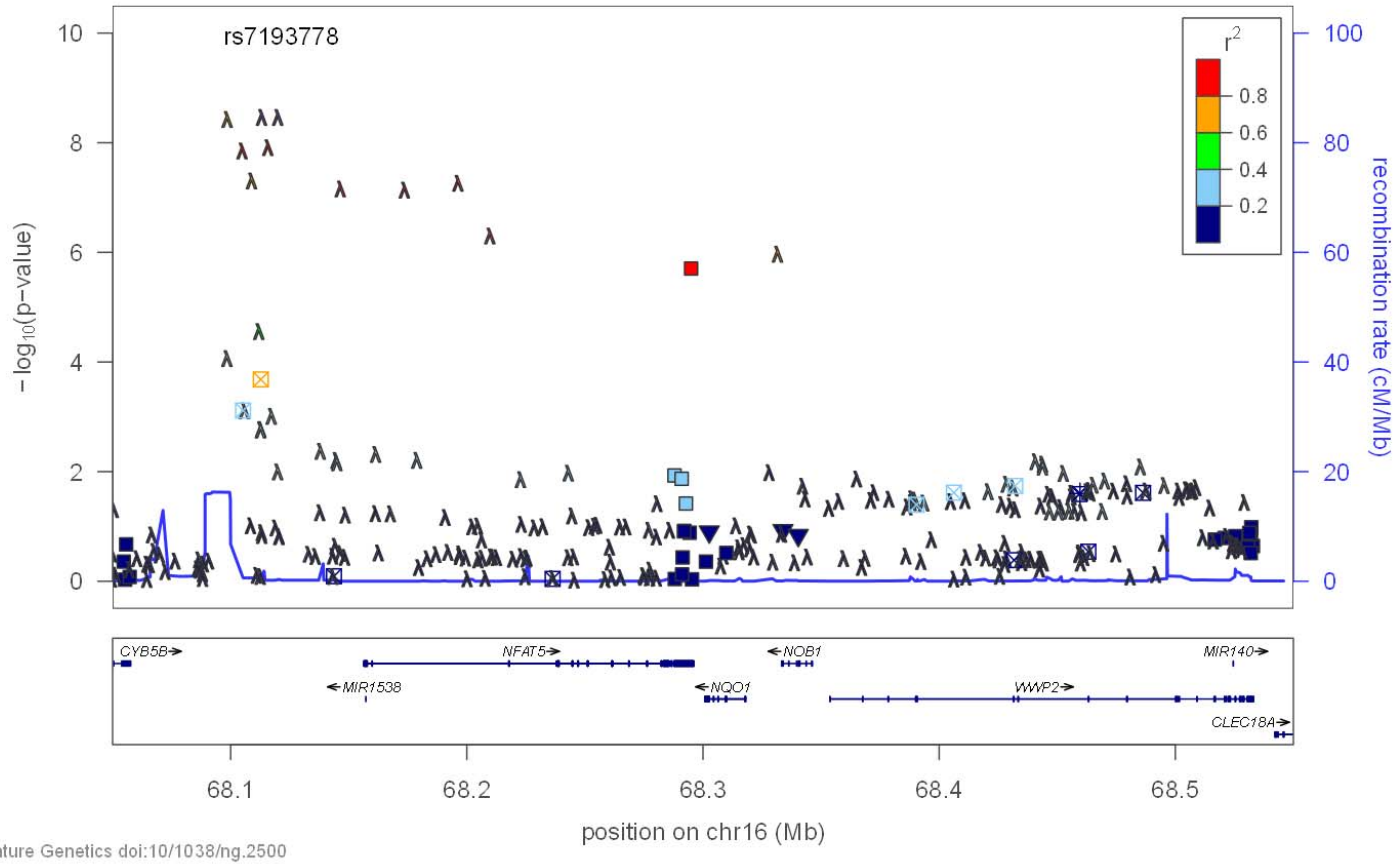

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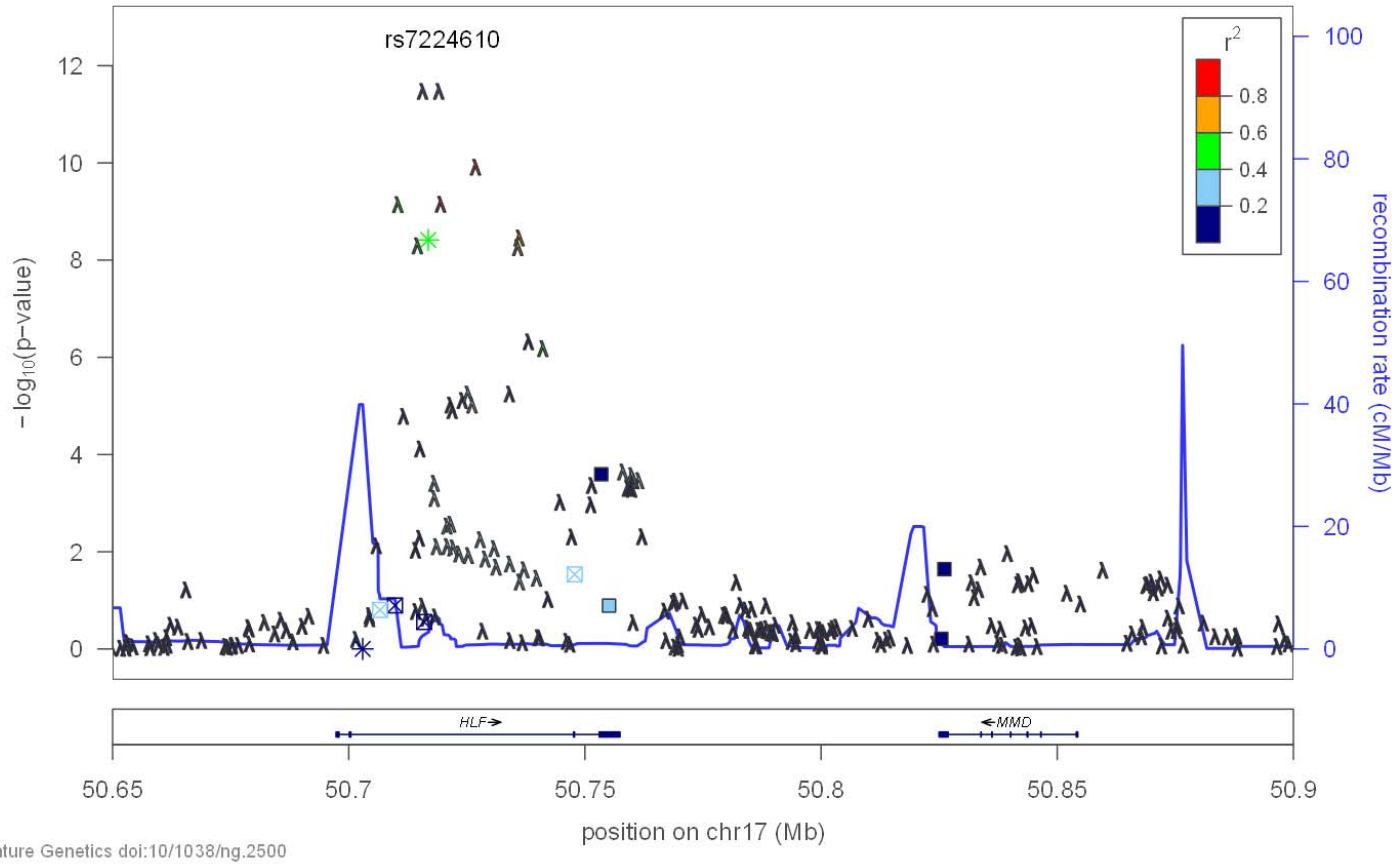

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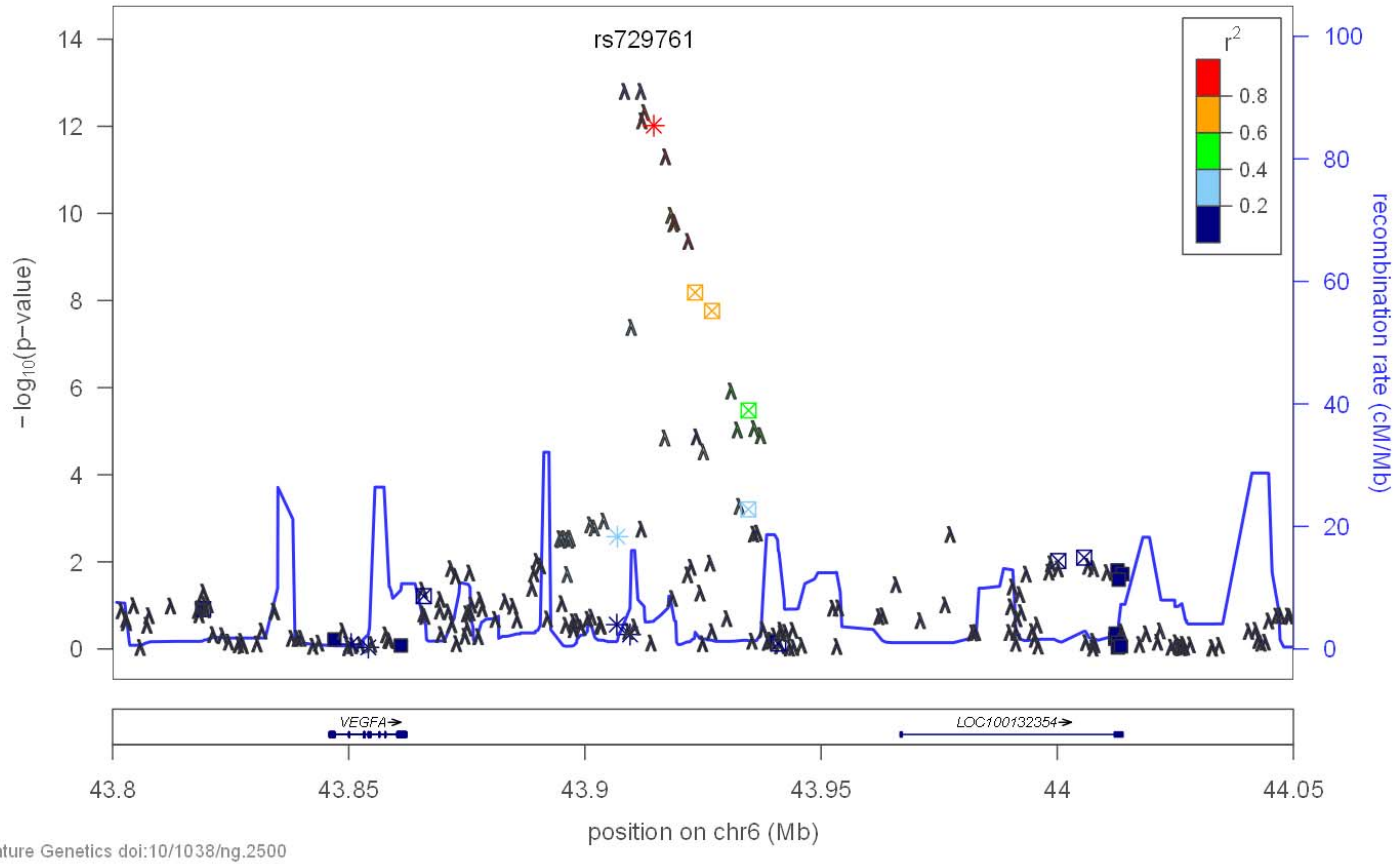
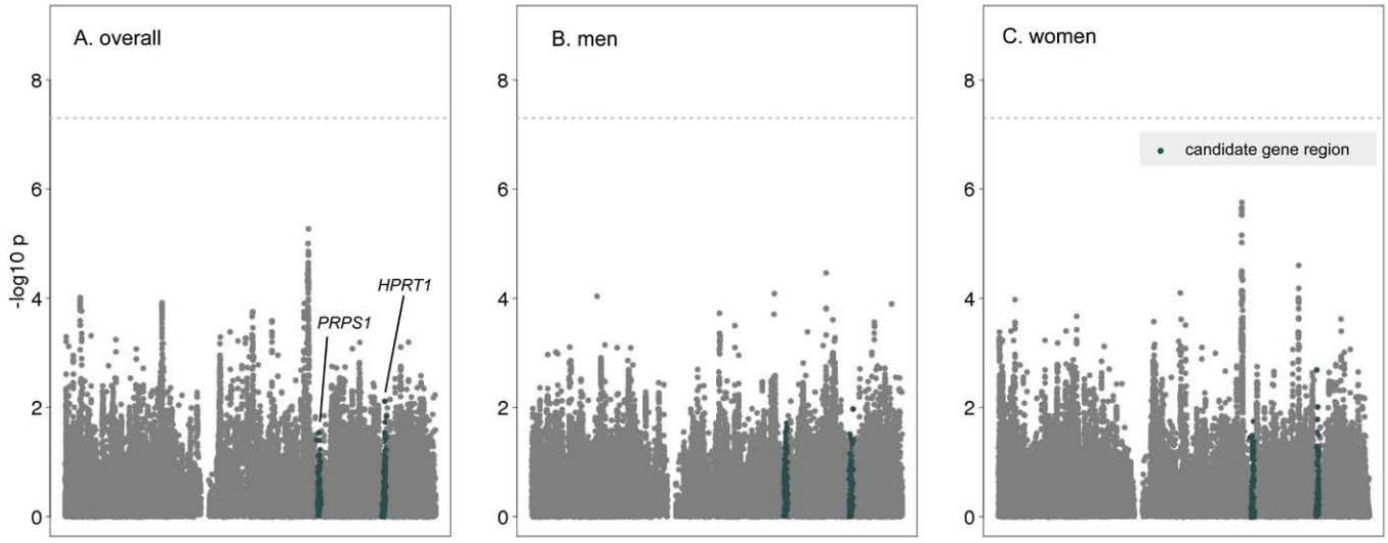


Nature Genetics doi:10/1038/ng.2500

Supplementary Figure 3: X Chromosomal Manhattan Plot

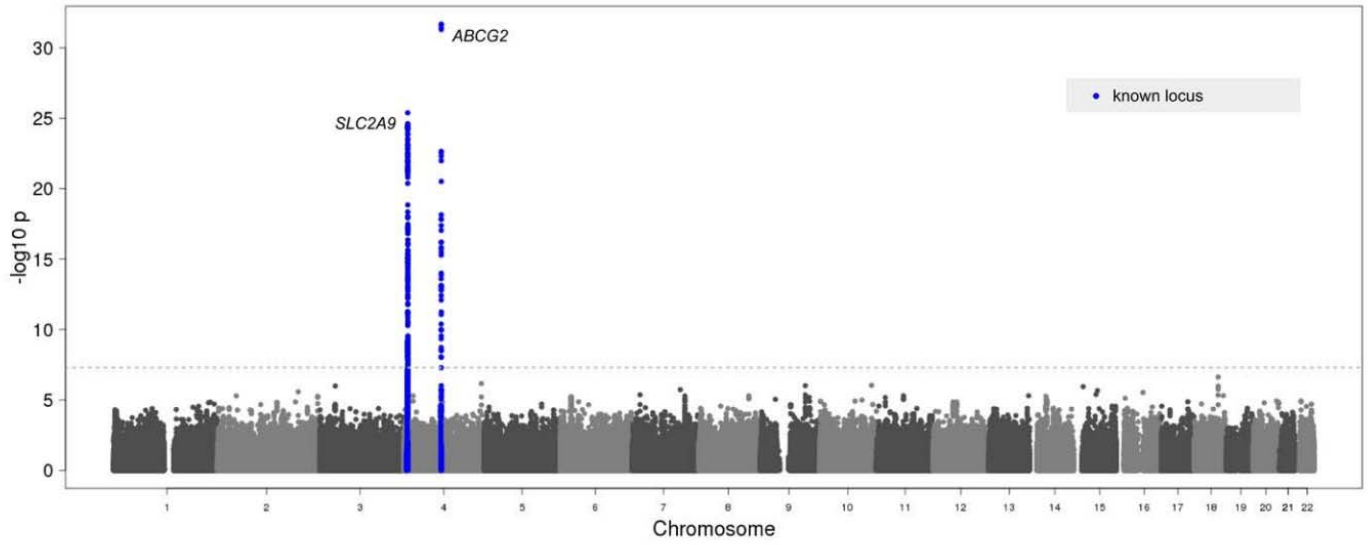
Manhattan Plot showing $-\log_{10}$ (p-values) for all SNPs analyzed within the serum urate X chromosome analysis ordered by their chromosomal position. Results are shown for A) the overall sample, separately in B) men and C) women. Green dots indicate the location of two candidate gene regions *PRPS1* (left) and *HPRT1* (right).



Nature Genetics doi:10/1038/ng.2500

Supplementary Figure 4: Manhattan Plot for Gout GWAS

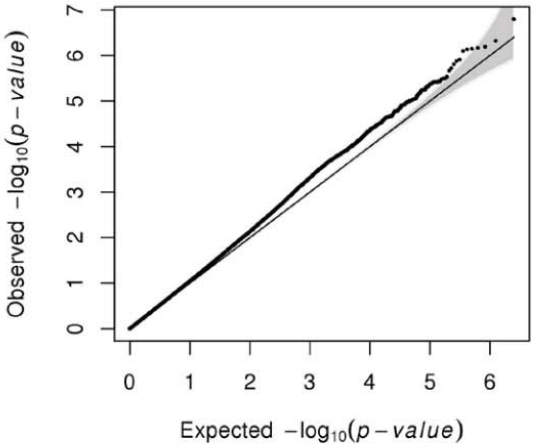
Manhattan plot showing $-\log_{10}$ (p-values) for all SNPs of the gout overall discovery GWAS ordered by their chromosomal position. Previously known loci are colored in blue.



Nature Genetics doi:10/1038/ng.2500

Supplementary Figure 5: QQ Plot for Gout GWAS

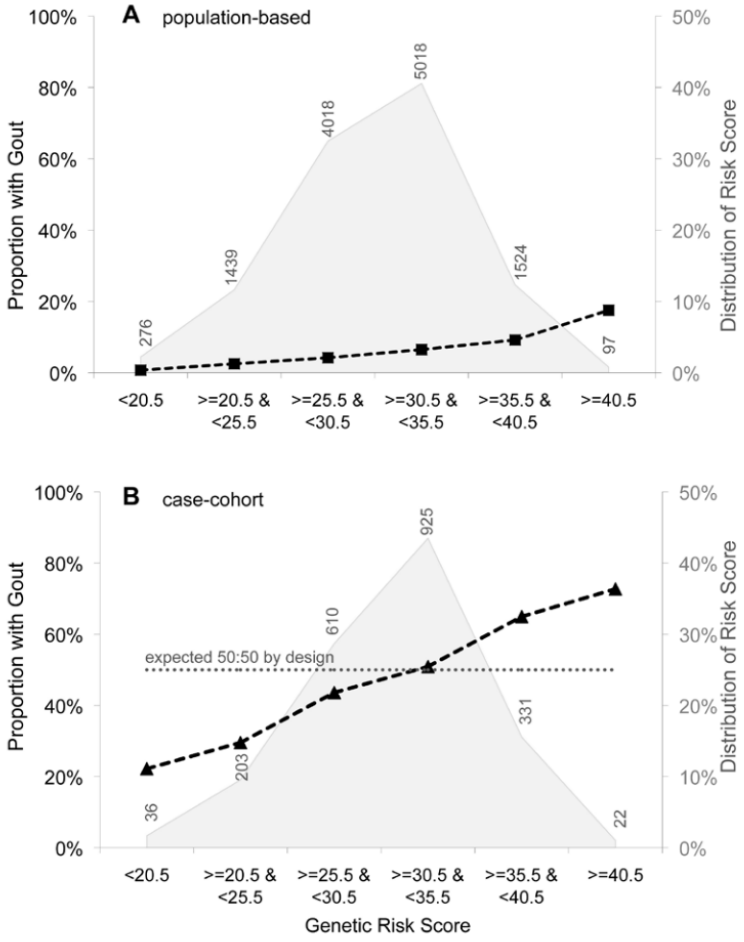
Quantile-quantile plot showing observed p-values of gout meta-analysis vs. expected p-values by chance after removal of SNPs within +/- 1.5 Mb of the index SNP in *SLC2A9* and +/- 1 Mb of the index SNPs at 9 additional known urate-associated loci. A second genomic control step was applied to correct for the post meta-analysis of =1.03.



Nature Genetics doi:10/1038/ng.2500

Supplementary Figure 6: Risk Score Figure

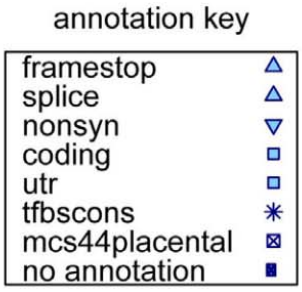
Showing the proportion of gout in relation to the computed genetic risk score in A) three population based studies (ARIC, KORA F4, and SHIP) and B) two nested case-cohort studies (HPFS and NHS).



Nature Genetics doi:10/1038/ng.2500

Supplementary Figure 7: Regional Association Plots for Network SNPs

Regional association plots showing $-\log_{10}$ (p-values) for all SNPs ordered by their chromosomal position within all regions of the network analysis as listed in **Table 2**. $-\log_{10}$ (p-values) correspond to the urate discovery GWAS. Each SNP is colored according to its correlation with the index SNP within the region as specified in the color scheme. Correlation structures correspond to HapMap 2 CEU r28. Gray color indicates unknown correlation. Data point symbols correspond to nonsense, non-synonymous, coding, UTR, splice variants, transcription factor binding sites and multi-species conservation according to dbSNP or the 1000 Genomes Project (August 2009 release)[1]. Plots are ordered by rs-number.



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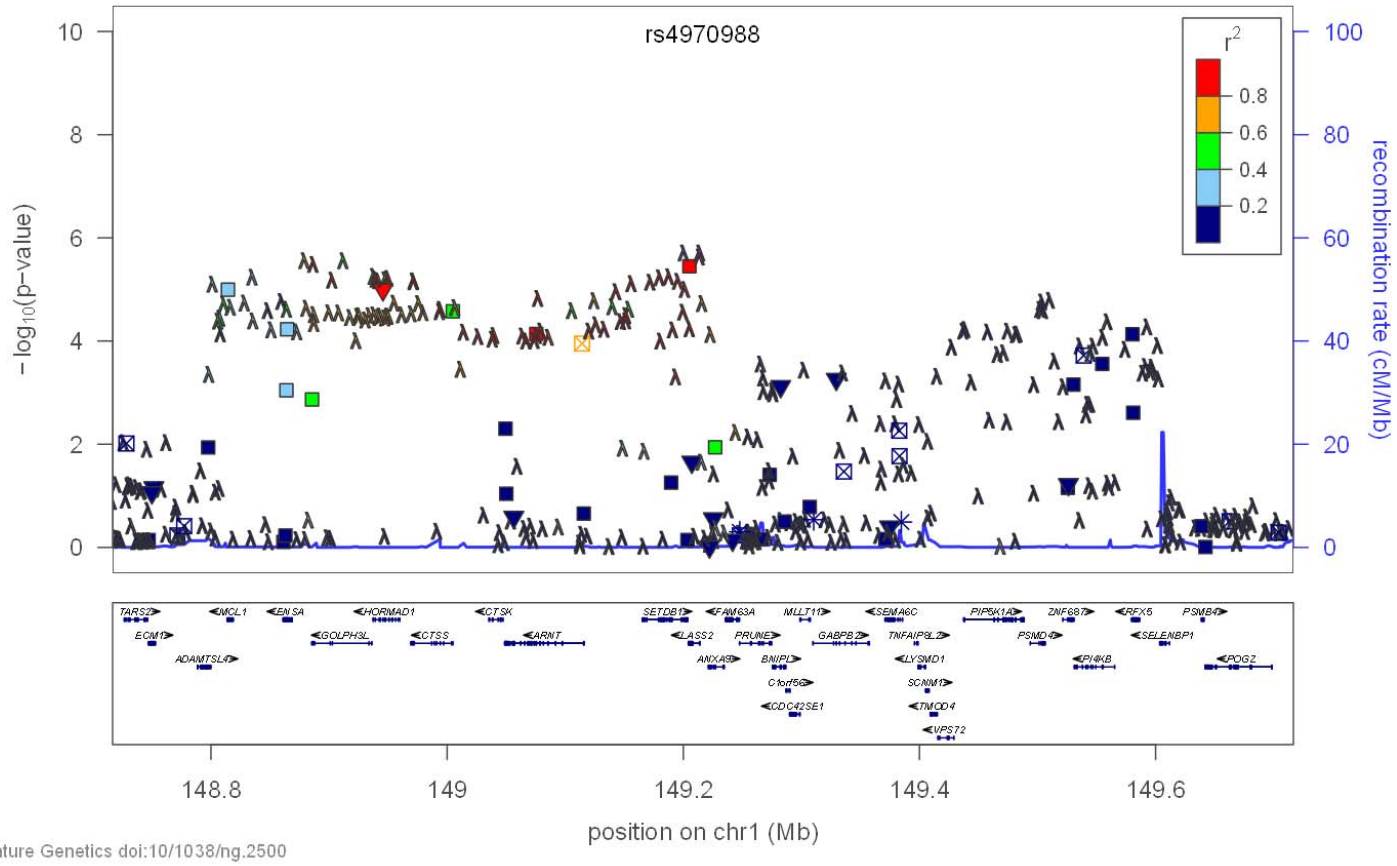

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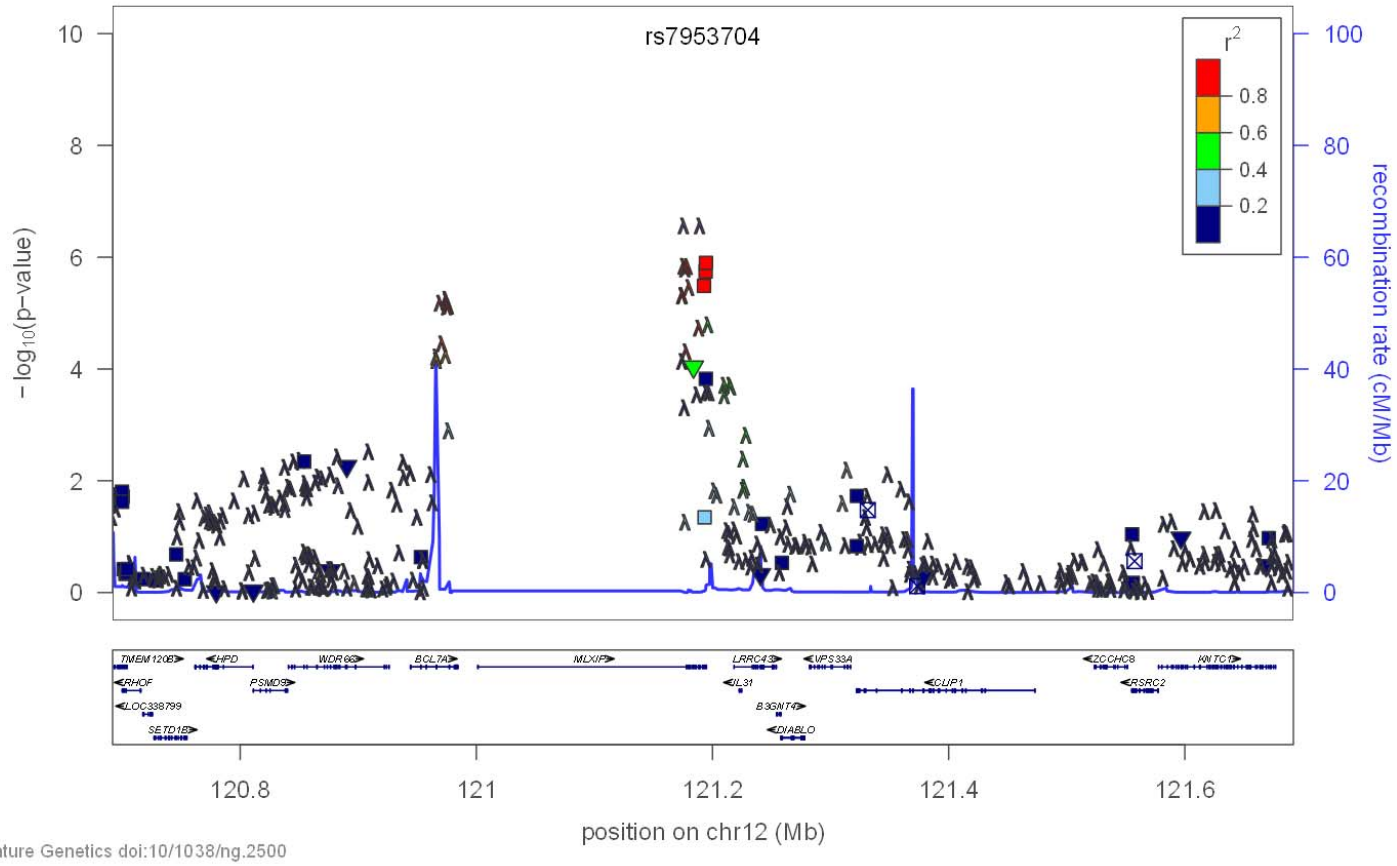

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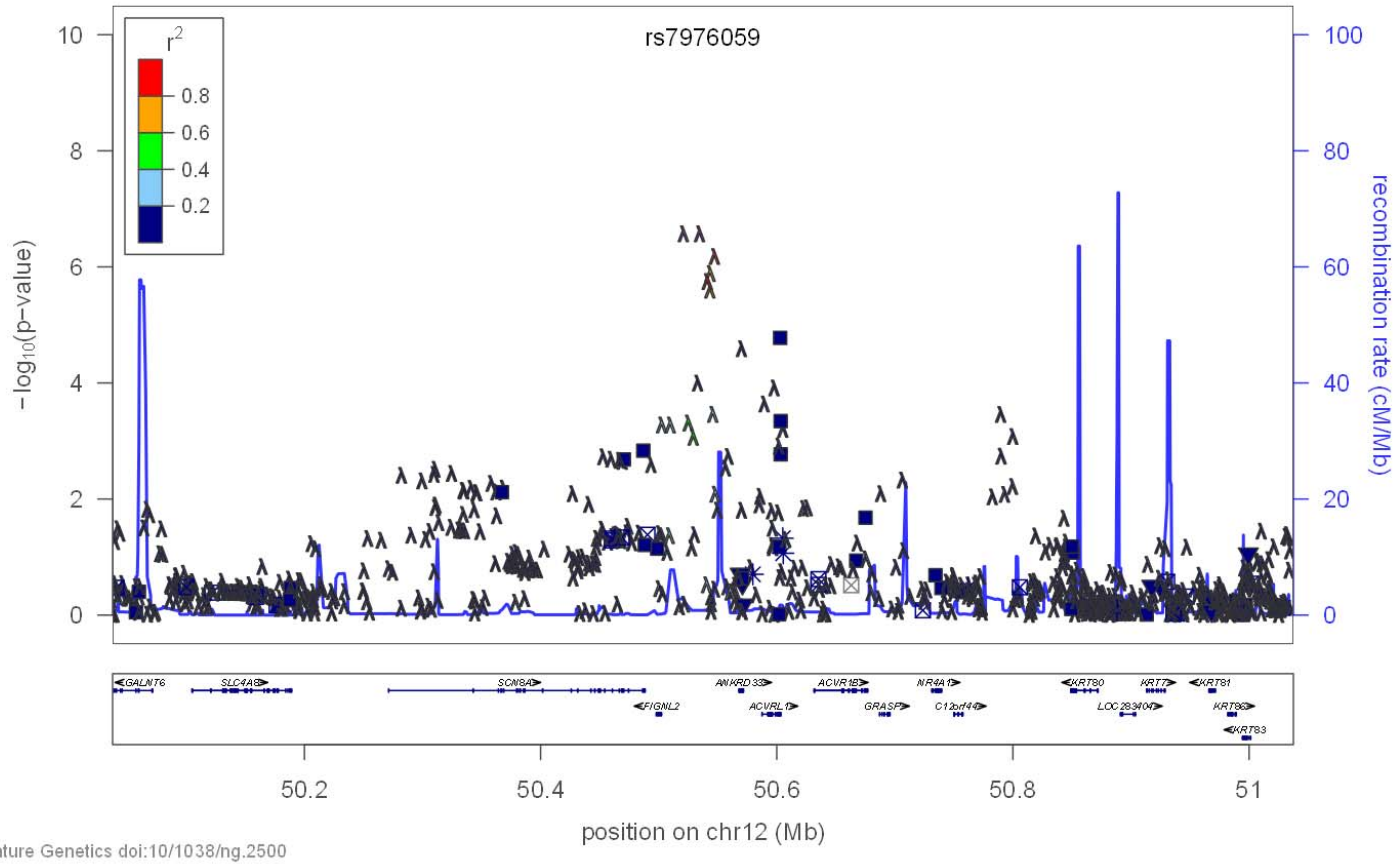
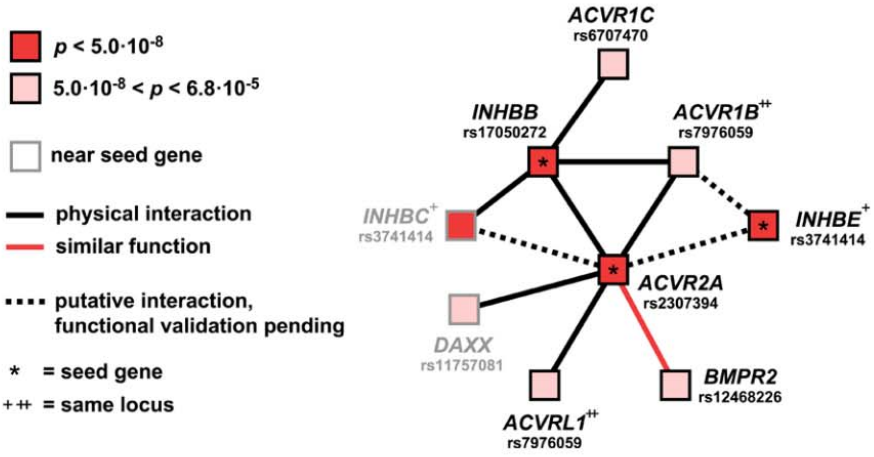


Nature Genetics doi:10/1038/ng.2500

Supplementary Figure 8: Inhibins-Activins Network

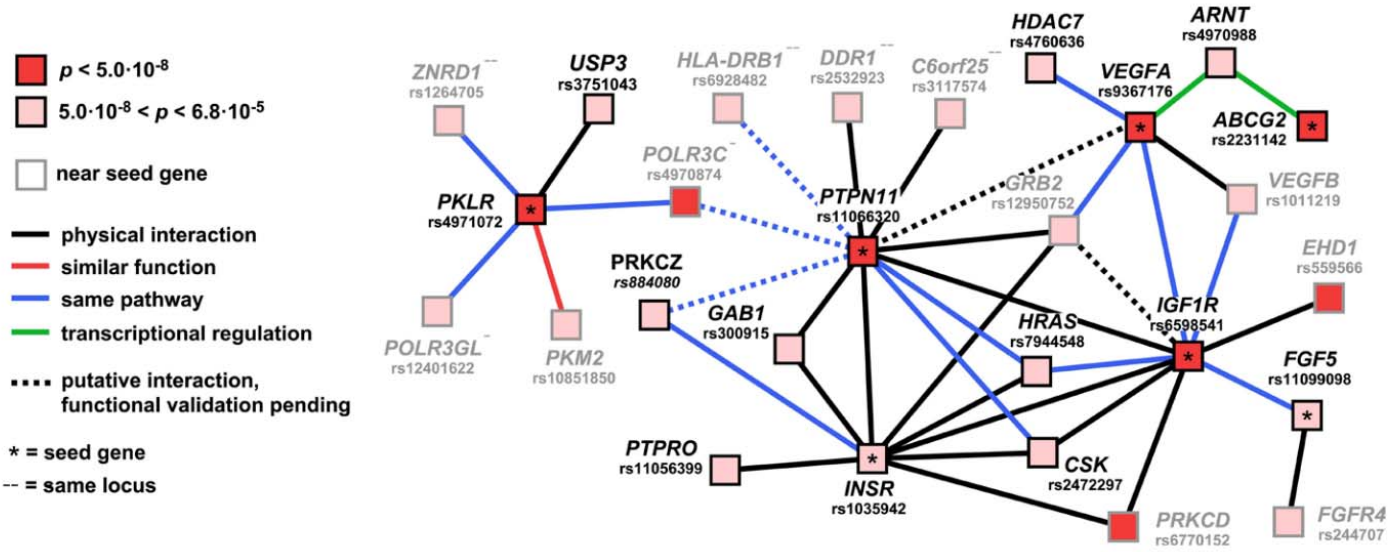
This figure highlights the interconnection of loci identified from serum urate GWAS analyses (seed genes, *) with those from the functional association network approach. Connections were formed between seed and other genes that contained urate-associated SNPs after multiple testing-correction. The evidence is based on i) physical interactions of the encoded proteins and ii) database interactions as provided by the STRING database. The listed rs numbers correspond to the index SNPs of seed genes or to the SNP with the smallest p-value in or near the implicated additional genes. Detailed information is provided in the **Supplementary Note (Pathway-based Analyses).**



Nature Genetics doi:10/1038/ng.2500

Supplementary Figure 9: Growth Factors Network

This figure highlights the interconnection of loci identified from serum urate GWAS analyses (seed genes, *) with those from the functional association network approach. Connections were formed between seed and other genes that contained urate-associated SNPs after multiple testing-correction. The evidence is based on i) physical interactions of the encoded proteins and ii) database interactions as provided by the STRING database. The listed rs numbers correspond to the index SNPs of seed genes or to the SNP with the smallest p-value in or near the implicated additional genes. Detailed information is provided in the **Supplementary Note (Pathway-based Analyses).**



Nature Genetics doi:10/1038/ng.2500

Supplementary Tables

Supplementary Table 1: Characteristics of the Analyzed Study Samples

(as used for the SNP association analyses)

Study	Sample Size (Urate Analysis)	Age (SD), years	Women, % (n)	Serum urate (SD), mg/dl	Gout, % (cases/overall)
Discovery cohorts					
AGES Reykjavik Study	3219	76.4 (5.5)	58.0 (1867)	5.97 (1.62)	4.3 (137/3219)
Amish	1139	49.8 (16.8)	48.1 (548)	4.2 (1.10)	NA
ARIC	9049	54.3 (5.7)	52.9 (4790)	5.94 (1.50)	5.4 (395/7300)
ASPS	845	65.2 (8.0)	43.2 (365)	5.32 (1.42)	6.0 (51/848)
AUSTWIN	11520	39.2 (17.2)	59.5 (6855)	4.85 (1.32)	NA
BLSA	521	70.6 (14.1)	47.8 (249)	5.21 (1.49)	4.4 (23/521)
BRIGHT	1743	56.9 (10.3)	60.4 (1053)	5.39 (1.44)	NA
CARDIA	1713	25.5 (3.3)	53.4 (914)	5.33 (1.37)	NA
CHS	3252	72.3 (5.4)	60.9 (1979)	5.50 (1.44)	5.1 (164/3192)
CoLaus	5409	53.4 (10.7)	52.9 (2863)	5.27 (1.42)	1.5 (79/5409)
CROATIA-KORCULA	895	56.2 (14.0)	63.9 (572)	4.92 (1.29)	4.7 (46/969)
CROATIA-SPLIT	490	49 (14.6)	57.9 (284)	4.80 (1.38)	3.2 (17/535)
CROATIA-VIS	912	56.4 (15.5)	57.7 (526)	5.23 (1.59)	6.4 (58/904)
DESIR	716	50.2 (8.2)	75.1 (538)	3.86 (0.92)	NA
EPIC-Norfolk cohort	1835	59.3 (9.0)	54.3 (997)	4.99 (1.37)	2.2 (54/2405)
ERF	889	49.6 (15.2)	60.7 (540)	5.52 (1.56)	1.1 (27/2385)
Estonian Biobank	931	39.4 (15.6)	50.8 (473)	4.95 (1.36)	0.9 (8/931)
Family Heart Study (FamHS)	3837	52.1 (13.7)	52.4 (2011)	5.42 (1.47)	NA
FHS	7699	37.9 (9.4)	53.1 (4089)	5.34 (1.51)	2.7 (197/7386)
Health 2000	2069	50.6 (11.0)	50.9 (1054)	5.17 (1.29)	NA
InCHIANTI	1205	68.2 (15.5)	55.5 (669)	5.08 (1.43)	1.9 (19/1005)
INCIPE	940	61.2 (11.5)	52.6 (495)	5.50 (1.45)	NA
INGI-Carlantino	432	49.9 (16.5)	61.3 (265)	4.90 (1.41)	NA
INGI-CILENTO	859	52.5 (19.4)	55.2 (474)	4.60 (1.59)	NA
INGI-FVG	1018	48.2 (19.7)	61.6 (627)	5.55 (1.57)	NA
INGI-Val Borbera	1658	54.7 (18.3)	55.8 (925)	5.02 (1.28)	2.3 (39/1658)
KORA F3	1643	62.5 (10.1)	50.5 (830)	5.21 (1.36)	6.3 (103/1644)
KORA F4	1814	60.9 (8.9)	51.3 (930)	5.37 (1.45)	6.3 (114/1810)
LBC1936	769	72.5 (0.7)	47.7 (367)	5.51 (1.47)	5.2 (40/769)
LifeLines	3343	55.5 (9.9)	59.2 (1980)	5.04 (1.25)	NA
LOLIPOP_EW_A	587	54.3 (10.4)	12.9 (76)	5.62 (1.32)	NA
LOLIPOP_EW_P	650	55.7 (9.1)	0 (0)	5.75 (1.35)	NA
LOLIPOP_EW610	924	55.9 (9.8)	26.9 (249)	5.30 (1.45)	NA
LURIC	963	62.0 (10.6)	27.8 (268)	5.04 (1.68)	NA
MICROS	1236	45 (16.8)	56.8 (702)	5.31 (1.42)	3.0 (39/1300)
NESDA	1731	42.3 (12.5)	67.9 (1176)	4.37 (1.17)	NA
NSPHS	655	47.0 (20.7)	52.8 (346)	5.38 (1.42)	NA
ORCADES	888	53.5 (15.7)	54.6 (485)	4.98 (1.20)	NA
PREVEND	3785	49.6 (12.4)	48.85 (1849)	5.12 (1.34)	NA

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PROCARDIS	3742	62.1 (7.0)	24.4 (913)	6.10 (1.46)	NA
RS-I	4274	70.1 (9.0)	61.6 (2633)	5.41 (1.37)	3.3 (196/5974)
RS-II	2123	64.8 (8.0)	54.4 (1155)	5.25 (1.28)	3.1 (66/2157)
SardiNIA	4694	43.3 (17.6)	56.3 (2643)	4.32 (1.48)	1.0 (49/4694)
SHIP	4067	49.7 (16.3)	50.7 (2064)	4.9 (1.4)	5.5 (211/3832)
SOCCS	1105	51.0 (5.7)	50 (553)	4.60 (1.25)	NA
Sorbs	896	47.2 (16.3)	59.6 (534)	5.80 (1.64)	NA
TwinsUK	3640	48.1 (12.9)	100 (3640)	4.49 (1.07)	NA
WGHS	NA	68.9 (7.3)	100 (23294)	NA	1.2 (290/23294)
Young Finns Study	2023	37.7 (5.0)	54.7 (1107)	4.74 (1.27)	NA
Total*	110347				3.0 (2115/69374)
Replication cohorts					
EPIC cases	793	59.3 (8.8)	58.4 (463)	5.51 (1.53)	3.4 (38/1130)
GHS I	2995	55.9 (10.9)	48.5 (1453)	4.83 (1.47)	NA
GHS II	1179	55.1 (10.9)	50.0 (590)	4.75 (1.47)	NA
GSK cases	819	50.9 (13.7)	66.3 (543)	5.00 (1.40)	NA
GSK controls	851	51.9 (13.2)	67.7 (576)	4.99 (1.34)	NA
HPFS	NA	59.1 (8.4)	0 (0)	NA	50.6 (717/1416)
Hunter Community Study	1088	65.9 (7.4)	51.1 (556)	5.37 (1.34)	NA
HYPEST	751	57.8 (9.8)	63.5 (477)	5.79 (1.50)	NA
KORA S2	3685	49.6 (14.1)	49.0 (1804)	4.93 (1.47)	2.5 (91/3681)
Lifelines replication	5031	43.2 (9.1)	56.1 (2823)	4.85 (1.21)	NA
LURIC replication GZ	804	59.0 (12.0)	34.0 (273)	5.0 (1.7)	NA
LURIC replication HD	1156	64.9 (9.2)	29.8 (344)	5.2 (1.7)	NA
MARS cases	636	48.4 (14.0)	52.7 (335)	5.19 (1.29)	NA
NHS	NA	55.8 (6.3)	100 (711)	NA	45 (319/711)
OGP (Ogliastra)	9556	49.6 (17.9)	56.1 (5558)	4.36 (1.48)	1.9 (187/9556)
OGP-Talana	1039	50.9 (19.1)	55.9 (581)	4.59 (1.64)	2.3 (20/862)
SAPALDIA asthmatics	570	51.3 (11.3)	52.5 (299)	5.31 (1.49)	NA
SAPALDIA non-asthmatics	874	52.9 (11.1)	50.1 (438)	5.25 (1.46)	NA
SHIP-Trend	986	50.1 (13.7)	56.2 (554)	4.79 (1.25)	NA
Samples of other ancestries					
LOLIPOP_IA317	2139	48.3 (10.5)	0	5.6 (1.3)	NA
LOLIPOP_IA610	5589	56.9 (10.0)	18.4 (1030)	5.6 (1.5)	NA
LOLIPOP_IA_P	612	51.1 (8.3)	0	5.5 (1.3)	NA
ARIC African American	2749	53 (5.8)	62.9 (1728)	6.3 (1.7)	8.3 (159/1908)
CARDIA African American	937	24 (3.8)	60.9 (571)	5.1 (1.3)	1.95 (18/923)
JHS African American	2134	50 (12.1)	60.8 (1297)	5.5 (1.7)	NA
BioBank Japan	15288	63.0 (11.7)	43.6 (6665)	5.4 (1.5)	NA

Study sample characteristics are presented for the sample with urate measurements if sample size for gout is different. *refers to the samples used in the main analyses.

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Supplementary Table 2: Study Sample Characteristics

Study Name	Study Design	Total Genotyped Sample Size	Exclusion Criteria for Study Participation or Disease Enrichment	Exclusions	Population Stratification	UA Measurement and QC	Gout Definition	Key Study References
Discovery Studies								
AGES Reykjavik Study	Prospective, population-based	3,219 of European ancestry	none	none	All individuals from Iceland, with no significant stratification within the population.	Serum urate was measured at the Icelandic Heart Association using the Roche-Hitachi P-Module instrument with Roche uricase method. The coefficient of variation for the urate assay was 4.3%.	Gout was determined from a positive answer on a questionnaire or if the participant was on allopurinol treatment at a study visit.	Harris et al. (2007)[2]
Amish Studies	Founder "healthy" population based[3].	European ancestry	none	none	NA	Serum UA levels drawn at the screening exam were assayed by Quest Diagnostics (Baltimore, MD) and measured to the nearest 0.1 mg/dl[4].	NA	Mitchell et al. (2008)[3], McArdle et al. (2008)[4]
Atherosclerosis Risk in Communities (ARIC) Study	Prospective, population-based[5]	9,713 of European ancestry	none	Of the 9713 genotyped individuals of European ancestry, we excluded 658 individuals based on discrepancies with previous genotypes, disagreement between reported and genotypic sex, one randomly selected member of a pair of first-degree relatives, or outlier based on measures of average DST or more than 8 SD away on any of the first 10 principal components.	Two principal components were associated with uric acid measurements and included as covariates in the regression.	UA was measured using the uricase method[6] at study visit 1. Repeated measurements of UA in 40 individuals, taken at least one week apart, yielded a reliability coefficient of 0.91, and the coefficient of variation was 7.2%[7].	Gout was defined by self-report at study visit 4 based on the question "did a doctor ever tell you that you had gout?".	ARIC (1989)[5], Iribarren et al. (1996)[6], Eckfeldt et al. (1994)[7]
Austrian Stroke Prevention	Prospective, population-based	923 genotyped Caucasians	no history or signs of stroke and dementia	Of the 923 genotyped individuals we excluded 67 subjects based on excess	Age and sex were included as covariates in the	UA was measured using the uricase method on a Hitachi	A subject was defined as having gout at	Schmidt et al. (1994)[8]

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Study (ASPS)		living in the city of Graz, Austria		autosomal heterozygosity, mismatch between called and phenotypic gender, or by being outliers identified by the IBD analysis. The final population for genetic analysis comprised 856 subjects. Additionally serum urate was not available in 3 cases.	regression	917 chemical analyzer at study visit 1. Reproducibility was assessed in 21 subjects and revealed a variation coefficient of 1.7%	study visit 1 if he/she reported a history of elevated uric acid levels and was currently treated for hyperuricemia.	
Australian Twin-Family Study (AUSTWIN)	Population-based, twin-pairs and their families	11,520 of European ancestry	none	Samples were excluded for less than 95% of SNPs successfully typed, sex or Mendelian errors, Non-European ancestry	Two principal components were included as covariates in the regression.	Serum uric acid was measured with the uricase method on a Roche 917 or Modular P analyser.	NA	Whitfield et al. (2002)[9], Middelberg et al. (2007)[10], Benyamin et al. (2009)[11]
Baltimore Longitudinal Study of Aging (BLSA)	Prospective, population-based	1,230	none	Of the 1230 genotyped subjects, genetic relatedness was assessed using PCA analysis using the HapMap population as reference. Out of the 857 subjects of European ancestry, 5 subjects were excluded for low genotyping (< 98.5%), 4 subjects were removed for sex misspecification. From the 848 subjects with European ancestry passing quality control, 718 subjects with uric acid data was used for this study.	Use top two principle components included as covariates in the regression model.	UA was measured using the uricase method (Johnson and Johnson, VITROS chemistry system).	NA	Shock et al. (1984)[12]
The BRItish Genetics of HyperTension (BRIGHT) study	Hypertensive cases from the BRIGHT study resource4.	1,743	Control exclusion criteria included BMI>35, diabetes, secondary hypertension or a co-existing illness. Blood pressure was measured using the OMRON-705CP blood pressure monitor.	Of 2000 cases typed, we excluded 257 people with poor genotype quality.	NA	Non-fasting blood samples were obtained from study participants and UA analyses was carried out on frozen serum stored at − 20 C. UA concentrations were measured using an uricase method on a Hitachi auto-analyser).	NA	Caulfield et al. (2003)[13]

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Coronary Artery Disease Risk in Young Adults (CARDIA)	Prospective, population-based	1,725 of European Ancestry	none	1 sex mismatch; 3 outliers in PCA; 1 discordant genotype	4 principal components included as covariates; none associated with UA	Serum uric acid was measured by the uricase method at multiple visits. The coefficient of variation of uric acid was 2.6%; the split sample technical error was 4.6%.	NA	Friedman et al. (1988)[14], The data collection forms used at each exam as well as the CARDIA protocols are available from the CARDIA website: http://www.cardia.dopm.uab.edu/em_dacf.htm
The Cardiovascular Health Study (CHS)	Prospective, population-based	3,329 CHS Caucasian participants	1908 persons were excluded due coronary heart disease, congestive heart failure, peripheral vascular disease, valvular heart disease, stroke or transient ischemic attack.	The present report is based upon genotyping results from 3,329 CHS Caucasian participants, who were free of clinical cardiovascular disease at baseline, consented to genetic testing, and had DNA available for genotyping. Genotypes were called using the Illumina BeadStudio software. Genotyping was successful in 3,291 persons.	Study sites (clinic sites) were included as covariates in the regression to account for population stratification.	Serum uric acid concentrations were measured at the baseline visit using the Kodak Ektachem 700 Analyzer with reagents (Eastman Kodak, Rochester, NY). The final study sample with available genotype and phenotype data consisted of 3,252 individuals for the analyses of uric acid.	Intake of previous or current gout-specific medication: colchicine, probenecid, or allopurinol. Total of 3,192 individuals for the analyses of gout.	Fried et al. (1991)[15]
Cohorte Lausannoise (CoLaus) Study	Population based	5,636 of European ancestry	none	Individuals with call rate below 90% were excluded. The younger of 1st/2nd degree related pairs were removed from the analysis.	First two ancestry principal components were used as covariates.	Serum uric acid was measured by uricase-PAP (1.0% - 0.5% maximum inter and intra-batch coefficients of variation).	Gout was indirectly defined: People taking allopurinol or colchicine.	Firmann et al. (2008)[16]
CROATIA-KORCULA	Cross-sectional, population-based	971	none	898 individuals left after QC based on genotyping quality, sex and ancestry check	None of the first 3 principal components strongly associated with uric acid; relatedness of participants taken into account using a mixed linear model with the polygenic effect set as random effect.	UA was measured using the uricase UV photometry method in "Labor Centar" biochemical lab, Bukovcev trg 3, 10000 Zagreb Croatia (www.laborcentar.hr).	Gout case based on self-report and medication; 46 cases	Zemunik et al. (2009)[17]
CROATIA-SPLIT	Cross-sectional, population-based	535	none	499 individuals left after QC based on genotyping quality, sex and ancestry check.	None of the first 3 principal components strongly associated	UA was measured using the uricase UV photometry method in "Labor Centar"	Gout case based on self-report and medication;17	Rudan et al. (2009)[18]

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					with uric acid; relatedness of participants taken into account using a mixed linear model with the polygenic effect set as random effect.	biochemical lab, Bukovcev trg 3, 10000 Zagreb Croatia (www.laborcentar.hr).	cases	
CROATIA-VIS	Cross-sectional, population-based	991	none	924 individuals left after QC based on genotyping quality, sex and ancestry check	None of the first 3 principal components strongly associated with uric acid; relatedness of participants taken into account using a mixed linear model with the polygenic effect set as random effect.	UA was measured using the uricase UV photometry method in "Labor Centar" biochemical lab, Bukovcev trg 3, 10000 Zagreb Croatia (www.laborcentar.hr). A subset of 774 samples had also been measured independently in the Institute for Clinical Chemistry and Laboratory Medicine, University Hospital Regensburg, Germany. Pearson correlation between the two urate measurements was 94% .	Gout case based on self-report and medication; 58 cases used in analysis	Vitart et al. (2006)[19]
Data from the Epidemiological Study on the Insulin Resistance Data from the Epidemiological Study on the Insulin Resistance Syndrome (DESIR) Study	Controls for the study of T2D and obesity selected from a population-based study.	716 of European ancestry	none	Using the STRUCTURE software, we identified 4 individuals of non-European ancestry. In order to minimize admixture bias in the rest of the DESIR participants, we excluded these individuals before analyses	none	UA was measured using the uricase method [20] at study visit 1. Repeated measurements of UA in 40 individuals, taken at least one week apart, yielded a reliability coefficient of 0.91, and the coefficient of variation was 7.2% [21].	NA	Balkau et al. (1997)[20], Vernay et al. (2004)[21]
European Prospective Investigation of Cancer (EPIC) Norfolk Study	Prospective, population-based, case-cohort design consisting of a random sample	3,850 of European ancestry	none	We excluded individuals who were duplicated samples DNA concordance >99%, cryptically related, related individuals DNA concordance >70% and	The 3552 individuals who were used for GWAS repeatedly showed no evidence of	Out of these individuals 2856 had uric acid measured, marked as serum L:89 H:1785 umol/L Olympus AU640.	Gout was defined as gout mentioned on hospital discharge records (ICD10	Day et al. (1999)[22], *http://www.srl.cam.ac.uk/epic/about/

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	(cohort) of 2566 participants at baseline and 1284 obese cases [22],*			<99%, ethnic outliers, and heterozygosity <23% or >30%. In the discovery analysis only controls were used. Obese cases were used for replication.	population stratification. Consequently, we have not adjusted for population stratification.		M10, between 1997-2008) or self-reported gout specific medication (colchicine, probenecid or allopurinol) at any follow-up.	
Erasmus Ruchphen Family (ERF) Study	Family based	2,385	none	none	Score test for association in related people implemented in R package GenABEL was used to control for family related ness.	UA concentrations were measured using an uricase/peroxidase method (DVIA1650-Autoanalyzer, Siemens Healthcare Diagnostics)	Gout was defined by intake of gout-specific medication: colchicine, probenecid or allopurinol	Pardo et al. (2005)[23]
Estonian Genome Center of University of Tartu (EGCUT)	Prospective, population-based	931 of European ancestry	none	Low genotyping quality (call rate <98%, MAF <1%, HWE p-value 10E-6); disagreement between reported and genotypic sex, one randomly selected member of a pair of first-degree relatives	Three principal components were associated with uric acid measurements and included as covariates in the regression.	UA was measured using the uricase method	Diagnosed at least by family doctor in ICD10 coding M.10	Nelis et al. (2009)[24], Metspalu et al. (2004)[25]
Family Heart Study (FamHS)	Population family-based [26]	4,135 of European ancestry		Quality control was performed before imputation. To assess Mendelian errors, we ran LOKI on our family data and removed 5,035 SNPs with Mendelian errors. We also removed 2 individuals that had an unaccepted number of Mendelian errors. As a final familial QC check, we used GRR software to check familial relationships based on IBS. Quality control procedures for SNPs included cleaning SNPs reported by Illumina as uninformative and unavailable on successive arrays (n=13,844), removing SNPs due to deviations from Hardy-Weinberg equilibrium	Ten principal components (EIGENSTRAT) were estimated using the genotype data of the largest sample of independent subjects (N= 753) and then applied to the family members. These principal components were included in the adjustment procedure of uric acid using stepwise regression analysis and held if they were significant at 5% level.	Uric acid was measured by a thin film adaptation of an uricase enzymatic method using the Vitros analyzer (Johnson & Johnson Clinical Diagnostics, Inc. Rochester NY 14650).	NA	Higgins et al. (1996)[26], Neogi et al.. (2011)[27], Neogi et al. (2009)[28], Tang et al. (2006)[29], Tang et al. (2003)[30], Wilk et al (2000)[31]

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				(p<1E-06) or SNPs with minor allele frequency <1% or >99% (n=22,088), and removing SNPs that are available in our data but not in HapMap (n=1,509). Additionally, 21 SNPs were designated as ambiguous and removed. After these quality control procedures, genotypes are available for 4,135 European American (EA) subjects with imputed genotypes for ~2.5 million SNPs.				
The Framingham Heart Study	Prospective, family based	9,274	none	Individuals with a sample call rate <97%, or heterozygosity > ±5 SD from the mean are excluded from association analyses.	Principal components of the genotypes of 550K SNPs were computed using the Eigenstrat software 5, and none of the first 10 components were found association with either urate levels or gout using a Bonferroni correction on alpha of 0.05, which indicated that there is little population admixture for these two traits and therefore no need to adjust for admixture in GWAS.	Serum urate was measured at the first examination cycle of each cohort using an autoanalyzer with a phosphotungstic acid reagent	Gout was ascertained via self-report in the Offspring subjects during exam cycles 3-7, and the first exam of the Third Generation	Dawber et al. (1963)[32], Crowley et al. (1964)[33]
Health 2000	Population-based	2,123 Finns	none	Samples with discrepancy between reported and genotypic sex were excluded. For pairs with pi_hat > 0.2 one of the pairs was excluded. Individuals with 0.05 < pi_hat < 0.2 to many other individuals were excluded.	NA	Uricase method, a colorimetric enzymatic method (Thermo Fisher Scientific, Vantaa, Helsinki).	NA	http://www.terveys2000.fi/doc/methodologyrep.pdf

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InCHIANTI study	Prospective, population-based	1,230 European ancestry	none	Of the 1231 genotyped subjects, 22 subjects were removed based on genotyping completeness (<97%), low heterozygosity (<0.3), or sex misspecification. 1205 subjects with uric acid data was used for the analysis.	Genomic Control	Plasma UA (mg/dl) was measured using an enzymatic-colorimetric method (Roche Diagnostics, GmbH, Germany). The lower limits of detection were 0.2 mg/dl, range 0.2–25.0 mg/dl, intra- assay and inter assay coefficients of variation (CV) were 0.5 and 1.7%, respectively.	NA	Ferrucci et al. (2000)[34]
INCIPE	Randomly chosen from the lists of patients of 62 randomly selected general practitioners (GPs) based in four geographical areas in the Veneto region, Northern Italy.	942 from Northern Italy	none	992 genotyped individuals (then 50 removed). Disagreement between reported and genotypic sex, one randomly selected member of a pair of first-degree relatives	From same geographical area	UA was measured using the UV uricase method; the between series CV is 1.5%	NA	Gambaro et al. (2010)[35]
INGI-Carlantino	Population-Based	659	none	Removed people with call rate <0.95 or too high IBS or heterozigosity. Removed people that did not pass sex chromosome checks or were < 18 years of age.	Corrected using mixed model regression analysis.	UA was measured with the colorimetric method using Targa 3000 from Biotecnica Instruments.	NA	Tepper et al. (2008)[36]
INGI-CILENTO	Population-Based study with pedigree information	859	none	Of the 859 participants who underwent genotyping, none was excluded	none	UA was measured using an enzymatic method.	NA	Ciullo et al. (2006)[37], Colonna et al. (2007)[38], Ciullo et al. (2008)[39], Sala et al. (2008)[40], Traglia et al. (2009)[41], Heid et al. (2009)[42], Colonna et al. (2009)[43], Bedin et al. (2009)[44], Siervo et al. (2010)[45]
INGI-FVG	Population-Based	1,471	none	Removed people with call rate <0.95 or too high IBS or heterozigosity. Removed people that did not pass	Corrected using mixed model regression analysis.	UA was measured with the colorimetric method using Targa 3000 from Biotecnica	NA	Girotto et al (2011)[46]

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				sex chromosome checks or were < 18 years of age.		Instruments		
INGI-Val Borbera	Family Population-based	1,665	none	Of the 1665 participants who underwent genotyping, we made the following exclusions: sample call rate <95% (n=1)	NA	UA was measured using HITACHI 917 ROCHE and Unicel Dx-C 800 BECKMAN	Gout was defined by self-report at study visit, or intake of gout specific medication	Traglia et al. (2009)[41]
KORA F3	Population-based	1,644	none	Only subjects with overall genotyping efficiencies of at least 93% were included. In addition the called gender had to agree with the gender in the KORA study database.	none	Non-fasting blood samples were obtained from study participants. UA analyses were carried out on fresh samples. UA concentrations were measured using an uricase method (URCA Flex, Dade Behring).	Current intake of urate-lowering medication	Wichmann et al. (2005)[47]
KORA F4	Population-based	1,814	none	Only subjects with overall genotyping efficiencies of at least 93% were included. In addition the called gender had to agree with the gender in the KORA study database.	none	Fasting blood samples were obtained from study participants. UA analyses were carried out on fresh samples. UA concentrations were measured using an uricase method (URCA Flex, Dade Behring).	Current intake of urate-lowering medication	Wichmann et al. (2005)[47]
LBC1936	Retrospective and prospective community-based cohort study[48]	1,005 of European ancestry	none	Individuals with a disagreement between genetic and reported gender were removed (n=12). Relatedness between subjects was investigated and, for any related pair of individuals, one was removed (PI_HAT (proportion of IBD) > 0.25, n=8). Samples with a call rate ≤ 0.95 (n=16), and those showing evidence of non-European descent by multidimensional scaling, were also removed (n=1).	None of the four extracted principal components were associated with uric acid measurements so were not included in the model.	Serum uric acid was determined using the VITROS URIC DT slide method performed using the VITROS URIC DT slide and the VITROS Chemistry products DT Calibrator Kit on VITROS DT60/DT60 II Chemistry systems (VITROS). This was performed at the Combined Biochemistry and Haematology Labs, Western General Hospital, Edinburgh.	Gout was defined by self-report based on the question "Any other disease or health problem?" or evidence of allopurinol in current medication.	Deary et al. (2007)[48], Houlihan et al. (2010)[49]

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LifeLines Cohort Study	Prospective, population-based	3,367 of European ancestry	none	Of the 3900 genotyped individuals, we excluded 533 individuals based on discrepancies with previous genotypes, disagreement between reported and genotypic sex, one randomly selected member of a pair of first-degree relatives, and non-European ancestry	NA	Uric acid was measured on a Roche/Hitachi Modular System (Roche Diagnostics GmbH), by the uricase/peroxida enzymatic method	NA	Stolk et al. (2008)[50]
London Life Sciences Population (LOLIPOP) study, LOLIPOP_EW610	Prospective, population-based	945		Duplicates, gender discrepancy, contaminated samples, relatedness	The first ten principal components were used as covariates in the regression.	Venous blood was collected into 5.0ml BD Vacutainer SST II Advance tube. Serum urate measurements were measured using the uricase method on Roche/Hitachi Cobas C 501 systems (USA).	NA	
London Life Sciences Population (LOLIPOP) study, LOLIPOP_EW_A	Prospective, population-based	878		Duplicates, contaminated samples, relatedness, samples already in EW610	The first ten principal components were used as covariates in the regression.	Venous blood was collected into 5.0ml BD Vacutainer SST II Advance tube. Serum urate measurements were measured using the uricase method on Roche/Hitachi Cobas C 501 systems (USA).	NA	Yuan et al. (2008)[51]
London Life Sciences Population (LOLIPOP) study, LOLIPOP_EW_P	Prospective, population-based	1,006		Duplicates, contaminated samples, samples already in EW610 and EW_A	The first ten principal components were used as covariates in the regression.	Venous blood was collected into 5.0ml BD Vacutainer SST II Advance tube. Serum urate measurements were measured using the uricase method on Roche/Hitachi Cobas C 501 systems (USA).	NA	Kooner et al. (2008)[52]
Ludwigshafen Risk and Cardiovascular Health Study (LURIC)	Prospective, case-control (CAD)	963	any acute illness other than ACSs, any chronic disease where non-cardiac disease predominated a history of malignancy within the past	Individuals with genotyping call rates below 0.96 were removed.	none	UA was measured using a photometric colour test (Harnsäure Farb-Reagenz, Greiner, Germany) on a Hitachi 717 at study entry.	Gout was defined by the recorded intake of anti-gout medication	Winkelmann et al. (2001)[53]

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			five years					
MICROS	Cross-sectional, population-based	1,345	none	1,268 individuals left after QC based on genotyping quality, sex and ancestry check.	None of the first 3 principal components strongly associated with uric acid but village of origin kept as cofactor; relatedness of participants taken into account using a mixed linear model with the polygenic effect set as random effect.	UA was measured using the uricase /peroxidase method.	Self-reported; 39 cases	Pattaro et al. (2007)[54]
Netherlands Study of Depression and Anxiety (NESDA)	Longitudinal cohort study of individuals with depressive and/or anxiety disorder	1,862 of western-European ancestry	Individuals were almost all cases with major depression or anxiety disorder (n=1705)	Ethnic outliers, XO and XXY samples, and samples with a call rate <95%, high genome-wide homo- or heterozygosity, excess IBS were excluded	none	UA was measured by enzymatic colorimetric test (uricase method, Roche Modular system). The coefficients of variation, over the complete measurement period, were 1.6% at a level of 0.25 mmol/l and 1.2% at a level of 0.55 mmol/l.	NA	Penninx et al. (2008)[55], Sullivan et al. (2009)[56]
NSPHS	Cross-sectional, population-based	700	none	656 individuals left after QC based on genotyping quality, sex and ancestry check	None of the first 3 principal components strongly associated with uric acid; relatedness of participants taken into account using a mixed linear model with the polygenic effect set as random effect.	UA was measured using the uricase /peroxidase method.	NA	Igl et al. (2010)[57]
ORCADES	Cross-sectional, population-based	920	of non-orcadian ancestry	889 individuals left after QC based on genotyping quality, sex and ancestry check.	None of the first 3 principal components strongly associated with uric acid; relatedness of participants taken	UA was measured using the uricase /peroxidase method in the Balfour Hospital, Kirkwall, UK. A subset of 718 samples had also been measured	Gout case based on self-report and medication; less than 50 cases	McQuillan et al. (2008)[58]

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					into account using a mixed linear model with the polygenic effect set as random effect.	independently in the Institute for Clinical Chemistry and Laboratory Medicine, University Hospital Regensburg, Germany. Pearson correlation between the two urate measurements was 99%.		
PREVEND	Prospective, population-based [59]	4,016 of European ancestry	none	Of the 4,016 genotyped individuals, we excluded 148 individuals based on discrepancies with previous genotypes, disagreement between reported and genotypic sex, first-degree relatives, or outlier based PCA.	none	Uric acid was measured in plasma and urine with the uricase PAP method as described previously (MEGA, Merck, Darmstadt, Germany). [60]	NA	Hillege et al. (2002)[59]
Procardis	Case-Control study of CAD	3,742	none	Dataset was prefiltered for individuals with success rate <95%, ancestory outliers on PCA, heterozygosity, IBC	Country of Origin was added as a covariate, population stratification was checked using PCA but was not adjusted for beyond Country of Origin.	Measured using uricase method in hospital clinical lab	NA	Broadbent et al. (2008)[61]
RS-I	Prospective, population based	5,974	none		none	Serum urate was measured at the baseline visit using a Kone Diagnostica reagent kit and autoanalyzer.	Using a computer network of pharmacies, data on medication prescription use was abstracted from pharmacies in the study region that registers all medication prescriptions beginning January 1, 1991. Participants	Hofman et al. (1991)[62], Hofman et al. (2009)[63]

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							receiving medication (allopurinol, benzbromarone, colchicine, and probenecid) were considered gout cases.	
RS-II	Prospective, population based	2,157	none		none	Serum urate was measured at the baseline visit using a Kone Diagnostica reagent kit and autoanalyzer.	Using a computer network of pharmacies, data on medication prescription use was abstracted from pharmacies in the study region that registers all medication prescriptions beginning January 1, 1991. Participants receiving medication (allopurinol, benzbromarone, colchicine, and probenecid) were considered gout cases.	Hofman et al. (1991)[62], Hofman et al. (2009)[63]
SardiNIA Study	Population-based study in Sardinia. The SardiNIA study consists of 6,148 individuals, males and females, ages 14-102 y, that were recruited from a cluster of four towns in the Lanusei	4,694	none	none	none	During physical examination, a blood sample was collected in the morning after the participants had been fasting for at least 12 h and after sitting for 15 min and divided into two aliquots. One was used for genomic DNA extraction and the second aliquot to characterize several	Diagnosis of gout was self-report by the participants during anamnesis based on the question "Have you ever been diagnosed with gout?"	Pilia et al. (2006)[64], Li et al. (2007)[65], Sanna et al. (2008)[66]

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	Valley of Sardinia. Samples have been characterized for several quantitative traits and medical conditions, including serum urate.					blood phenotypes, including evaluation of serum UA. UA (mg/dl) was measured using enzymatic–colorimetric methods (Bayer) The lower limits of detection were 0.2 mg/dl, range 0.2–25.0 mg/dl, intra-assay and inter assay coefficients of variation were equal to 0.5% and 1.7%, respectively.		
Study of Health in Pomerania (SHIP)	Population-based	4,081 of European ancestry	none	24 individuals identified as duplicated or with reported/genotyped gender mismatch	none	Uricase method, a colorimetric enzymatic method (Uric acid PAP, Boehringer) from non-fasting, fresh serum	Gout was defined by self-report at study visit on the question: Did you have any of the following diseases in the last 12 months? Gout or increased uric acid levels?	John et al. (2001)[67], Völzke et al. (2011)[68]
SOCCS	Colorectal cancer case control study, population-based	2,024	none	1,984 individuals after QC, 1,105 of whom had uric acid phenotypes.	No PCs of ancestry included in analysis	UA was measured using the uricase /peroxidase method.	Self-reported information "Up until a year ago had you ever had any other serious illness, chronic condition or mental health condition?". 3 cases. Less than 50 cases.	Tenesa et al. (2008)[69]
Sorbs	Population-based	1,020	46 individuals excluded as they were on a medication that lowers serum uric acid	ethnic outliers, duplicates, and gender mismatches	Estimation of kinship matrix to take account of relatedness.	enzymatic color test (Roche Diagnostics, Inc)	NA	Tönjes et al. (2009)[70], Tönjes et al. (2010)[71], Veeramah et al. (2011)[72]
TwinsUK	Twins	5,654 of European ancestry	none	Samples: Exclusion criteria were: (i) sample call rate <98%, (ii) heterozygosity	Estimation of kinship matrix to take account of	Ektachem/Vitros system, Johnson & Johnson Clinical	NA	Moayyeri et al. (2012)[73]

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				across all SNPs >2 s.d. from the sample mean; (iii) evidence of non-European ancestry as assessed by PCA comparison with HapMap3 populations; (iv) observed pairwise IBD probabilities suggestive of sample identity errors; (v). We corrected misclassified monozygotic and dizygotic twins based on IBD probabilities.	relatedness.	Diagnostics		
Women's Genome Health Study	Prospective, population based	23,294 with verified European ancestry	none	none	No principal component was significant.	NA	Gout was defined by self-report on any follow-up questionnaire based on the question "In the past year, have you been diagnosed with gout?" ICD9 codes 274.0, 274.1, 274.8, 274.9	Ridker et al. (2007)[74]
Young Finns Study	Birth cohort follow-up	2,443 Finns	none	Samples with discrepancy between reported and genotypic sex were excluded. For pairs with pi_hat > 0.2 one of the pairs was excluded. Individuals with 0.05 < pi_hat < 0.2 to many other individuals were excluded.	none	Uricase method, a colorimetric enzymatic method (Thermo Fisher Scientific, Vantaa, Helsinki).	NA	Raitakari et al. (2008)[75]
***In Silico* Replication Studies**								
EPIC - cases	See description above.							
GSK cases/controls	Case-control study for unipolar depressive disorder	819 cases/ 851 controls of European ancestry	GSK cases: patients with unipolar recurrent depression, exclusion criteria: presence of	MDS-analysis revealed no outliers (more than 8SD away on any of the first 10 principal components): after QC 819 cases/851 controls.	No principal component was associated with uric acid so none was included as covariates. No principal component was	UA was measured using the uricase method (Roche/Hitachi cobas c system, UA ver.2).	Information on gout was not obtained.	Lucae et al. (2006)[76], Kloiber et al. (2010)[77], Kohli et al. (2011)[78]

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			manic or hypomanic episodes, mood incongruent psychotic symptoms, lifetime diagnosis of drug abuse and depressive symptoms secondary to alcohol or substance abuse or dependence or to a medical illness or medication GSK controls: exclusion criteria: anxiety and affective disorders.		associated with uric acid so none was included as covariate.			
Gutenberg Health Study (GHS I + II)	Population-based	4860 (3422 (GHS I) + 1438 (GHS II))	age below 35 and above 74	Of the 4860 we excluded 685 (426 + 259) based on a call rate less than 97 %, a rate of heterorzygosity 3 standard deviations away from the mean, disagreement between reported and genotypic sex, estimated IBD > 0.25, IBS based principal components.	none	UA was measured using the uricase method at study visit during routine meausrements. Intra coefficient of variation (CV) was 0% at a mean value of 4.9 mg/dL and 0.44% at a mean value of 9.52 mg/dL, the inter CV% was 2.25% at a mean value of 4.9 mg/dL, and 0.97% at a mean value of 9.4 mg/dL.	NA	Zeller et al. (2010)[79], Wild et al. (2010)[80], Wild et al. (2011)[81]
Hunter Community Study (HCS)	Prospective, population-based	1,230 of European ancestry	none	Individuals were excluded for genotype call rate <95%, discrepancies between clinical and inferred gender, one randomly selected member of a pair of first- or second-degree relatives or clear evidence of non-European	No principal components were associated with uric acid, and were not included as covariates.	The HAPS pathology service did the urate measurements. They are a NATA accredited lab and meet national standards for quality assurance.	Gout was defined by self-report use of "Gout medication".	McEvoy et al. (2010)[82]

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				ancestry in Eigenstrat PCA.				
LifeLines Cohort Study	Prospective, population-based	5,031 of European ancestry	none	none	NA	Uric acid was measured on a Roche/Hitachi Modular System (Roche Diagnostics GmbH), by the uricase/peroxidase enzymatic method.	NA	Stolk et al. (2008)[50]
Ludwigshafen Risk and Cardiovascular Health Study (LURIC)	Prospective, case-control (CAD)	1,960	any acute illness other than ACSs, any chronic disease where non-cardiac disease predominated a history of malignancy within the past five years	Individuals which were part of the discovery analysis were removed. Samples were also removed because of gender discrepancy, relatedness or low call rate (<90%).	Sample HD (Heidelberg) n=1156 and GZ (Graz) n=804 were analyzed separately.	UA was measured using a photometric colour test (Harnsäure Farb-Reagenz, Greiner, Germany) on a Hitachi 717 at study entry.	Gout was defined by the recorded intake of anti-gout medication	Winkelmann et al. (2001)[53]
MARS cases	Case-control study for depressive disorder	643 cases of European ancestry	MARS cases: patients with depressive episode, exclusion criteria: depressive disorders caused by a medical or neurologic condition and alcohol or substance dependence.	MDS-analysis revealed 7 outliers (more than 8SD away on any of the first 10 principal components): after QC: 636 cases.	No principal component was associated with uric acid so none was included as covariates. No principal component was associated with uric acid so none was included as covariate.	UA was measured using the uricase method (Roche/Hitachi cobas c system, UA ver.2).	Information on gout was not obtained.	Kohli et al. (2011)[78]
Ogliastra Genetic Park - Talana	Population-based study with pedigree information	860	none	none	none	Uric acid levels were measured using the uricase method with an automated TARGA BT-3000 Chemistry Analyser	Gout was defined by self-report at study visit based on the question "did a doctor ever tell you that you had gout?".	Portas et al. (2010)[83], Biino et al. (2010)[84], Tore et al. (2011)[85]
Study of Health in Pomerania -	Population-based	986 of European ancestry	none	array call rate < 94%, individuals identified as duplicated or with	none	UA was measured from non-fasting, fresh serum. An	Gout was defined by self-report at study	John et al. (2001)[67], Völzke et al. (2011)[68]

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Trend (SHIP-Trend)				reported/genotyped gender mismatch		Uricase methode was used on a Dimension Vista® System (SIEMENS, Eschborn, Germany). The coefficient of variation was 1.92% at low level of control material (mean value = 291 mol/L).	visit on the question: Did you have any of the following diseases in the last 12 months? Gout or increased uric acid levels?	
Swiss Cohort Study on **A**ir **P**ollution **A**nd **L**ung and Heart **Di**seases in **A**dults	Prospective, population-based	1,640	asthmatics and non-asthmatics separate	28 failed genotyping, 35 low call rate (<97%), 17 non-European descent, 64 cryptic relatedness, 26 overlap with ECRHS, 12 males with high X-heterozygosity, 1 sex inconsistency, 13 missing UA levels (=1444 included in this analysis)	Two principal components were included as covariates in the regression.	Uric acid concentrations were determined by a colorimetric uricase/peroxidase method using reagents and the Modular P autoanalyser from Roche diagnostics (Rotkreuz, Switzerland). At concentrations of 203 micromol/l and 355 micromol/l the inter assay imprecision was 1% or less.	NA	Martin et al. (1997)[86], Ackermann-Liebrich et al. (2005)[87]
De Novo Replication Studies								
HYPertension in ESTonia (HYPEST)	Hypertensive cases recruited at the clinics and population-based controls [88-90]	758 of European (Estonian) ancestry	none	none	none	The venous blood for serum biomarker analysis was drawn in the morning after an overnight fast [88,90]. UA was measured by standardized assays (Cobas Integra 800Ò analytical platform, Roche Diagnostics, Inc.) at the United Laboratories, Tartu University Clinics or at the Diagnostics Division Laboratory, the North Estonia Medical Centre [90]. EURACHEM guidelines were applied to	NA	Ong et al. (2011)[88], Ong et al.(2009)[89], Juhanson et al.(2008)[90]

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						estimate measurement uncertainty (9.7%).		
KORA S2	Population-based	3,685	none	Only subjects with overall genotyping efficiencies of at least 93% were included.	none	Non-fasting blood samples were obtained from study participants. UA analyses were carried out on fresh samples. UA concentrations were measured using an uricase method (Technicon, SMAC AutoAnalyzer).	Current intake of urate-lowering medication	Wichmann et al. (2005)[47]
Ogliastra Genetic Park	Population-based study with pedigree information	9,704 of Sardinian ancestry	none	Individuals with a call rate <0.9 in de novo genotyping were excluded.	Study center was included as covariate in the regression	UA was measured in MG/DL units using TARGA 3000 with enzymatic colorimetric uricase method.	NA	Portas et al. (2010)[83], Biino et al. (2009)[84], Pistis et al. (2009)[91]
Studies with FEUA and UUCR that are not included above								
Hercules	Population based	374	none	Individuals with call rate below 90% were excluded. The younger of 1st/2nd degree related pairs were removed from the analysis.	First two ancestry principal components were used as covariates.	Uric acid was measured by uricase-PAP (1.0% - 0.5% maximum inter and intra-batch coefficients of variation).	NA	Bochud et al. (2009)[92]
Incident gout studies								
Nurses Health Study (NHS)	Gout case-control study nested within a prospective cohort (NHS)	2,275 (NHS + HPFS)	Gout cases and their matched controls	79 ids from NHS and HPFS together were removed after relatedness check, 76 ids were duplicates and 3 were removed from siblings set with high SNP missingness rate, 69 ids that did not cluster with other self-identified US whites were removed.	The top three principal components of genetic variation were included as covariates in the logistic and linear regressions.	UA was measured using the uricase method (Data not included as this analysis for gout).	Gout was defined by the American College of Rheumatology criteria for gout.	Choi et al. (2004)[93], Choi et al. (2004)[94], Choi et al. (2008)[95]
Health Professionals Follow-Up Study (HPFS)	Gout case-control study nested within a prospective cohort (HPFS)	2,275 (NHS + HPFS)	Gout cases and their matched controls	79 ids from NHS and HPFS together were removed after relatedness check, 76 ids were duplicates and 3 were removed from siblings set with high SNP missingness rate, 69 ids that did not cluster with	The top three principal components of genetic variation were included as covariates in the logistic and linear regressions.	UA was measured using the uricase method (Data not included as this analysis for gout).	Gout was defined by the American College of Rheumatology criteria for gout.	Choi et al. (2010)[96], Choi et al. (2010)[97]

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				other self-identified US whites were removed.				
Study Samples of Indian Ancestry								
London Life Sciences Population (LOLIPOP) study, LOLIPOP_IA317	Prospective, population-based	2,694	none	Duplicates, gender discrepancy, contaminated samples, relatedness, samples already in IA610	The first ten principal components were used as covariates in the regression.	Venous blood was collected into 5.0ml BD Vacutainer SST II Advance tube. Serum urate measurements were measured using the uricase method on Roche/Hitachi Cobas C 501 systems (USA).	NA	Chambers et al. (2008)[98]
London Life Sciences Population (LOLIPOP) study, LOLIPOP_IA610	Prospective, population-based	7,032	none	Duplicates, gender discrepancy, contaminated samples, relatedness	The first ten principal components were used as covariates in the regression.	Venous blood was collected into 5.0ml BD Vacutainer SST II Advance tube. Serum urate measurements were measured using the uricase method on Roche/Hitachi Cobas C 501 systems (USA).	NA	Chambers et al. (2008)[98]
London Life Sciences Population (LOLIPOP) study, LOLIPOP_IA_P	Prospective, population-based	1,005	none	Duplicates, contaminated samples, samples already in IA610 and IA317	The first ten principal components were used as covariates in the regression.	Venous blood was collected into 5.0ml BD Vacutainer SST II Advance tube. Serum urate measurements were measured using the uricase method on Roche/Hitachi Cobas C 501 systems (USA).	NA	Kooner et al. (2008)[52]
Study Samples of African American Ancestry								
ARIC	Population-based	2,749	not self-identified as black	Data cleaning conducted centrally at the Broad Institute	Adjustment for the first 10 principle components	Serum urate concentrations were measured with the uricase method at visit 1	Gout status was ascertained from a questionnaire at visit 4.	Iribarren et al. (1996)[6]
CARDIA	Population-based	937	none	Data cleaning conducted centrally at the Broad Institute	Adjustment for the first 10 principle components	Serum urate was measured at baseline using the uricase method.	Gout was self-reported at follow-up visits at 7, 10, and 15 years	Friedman et al. (1988)[14]
JHS	Population-based	3,443	none	Data cleaning conducted centrally at the Broad Institute	Adjustment for the first 10 principle components	Baseline serum urate was measured using the uricase method.	NA	Taylor et al. (2005)[99], Fuqua eta al. (2005)[100]
Study Samples of Japanese Ancestry								

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The BioBank Japan Project	Disease patients cohort [101]	15,288 of Japanese disease patients affected with each of the 21 diseases [101-103].	none	The following subjects were excluded.(i) low call rate (<98%), (ii) in 1st or 2nd kinships, (iii) outliers from East-Asian clusters in the result of principal component analysis (PCA) performed with HapMap Phase II populations, (iv) serum urate, sex, or age were not available, (v) age <18, age > 85, with dialysis treatment or with kidney failure.	Subjects who were determined to be of non-Japanese origin by self-report or by PCA were excluded. No principal component was included as covariate in the regression.	UA levels were obtained from medical records of the medical institutes which participated in the BioBank Japan Projects.	No information on the affection status of gout was obtained.	Nakamura et al. (2007)[101], Kamatani et al. (2010)[102], Okada et al. (2011)[103]

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Supplementary Table 3: Study-specific Genotyping Information

Study	Array type(s)	Genotype calling	QC filters for genotyped SNPs used for imputation	No of SNPs used for imputation	Imputation	Imputation Backbone (NCBI build)	Filtering of imputed genotypes	Data management and statistical analysis	inflation factor urate overall
AGES Reykjavik Study	Illumina Hu370CNV	Illumina BeadStudio	call rate <97%, MAF<1%, pHWE <10E-6	308,340	MACH v1.0.16	HapMap release 22 (build 36)	none	ProbABEL, PLINK, R	1.05
Amish	Affymetrix 500K, Affymetrix 6.0	BRLMM	call rate <95%, MAF<1%, pHWE <10E-6	338,598	MACH v1.0.15	HapMap release 22 (build 36)	none	Measured genotype accounting for polygenic component	1.03
ARIC	Affymetrix 6.0	Birdseed	call rate <95%, MAF<1%, pHWE <10E-5	669,450	MACH v1.0.16	HapMap release 22 (build 36)	none	ProbABEL, PLINK, R	1.02
ASPS	Illumina Human 610-Quad BeadChip	Illuminus software	call rate <97.5%, MAF <1%, , pHWE <1E-6	550,635	MACH v1.0.15	HapMap release 22 (build 36)	none	SPSS, ProbABEL, R	1.01
AUSTWIN	Illumina 370, Illumina 610	BeadStudio-gencall v3.0	call rate <95%, MAF <1%, pHWE <10E-5	269,840	MACH v1.0.15	HapMap release 22 (build 36)	r2 ≥ 0.3	MERLIN v1.1.2, PLINK v1.07	1.04
BLSA	Illumina 550K	BeadStudio	call rate <99%, MAF <1%, pHWE < 10E-4	501,704	MACH v1.0.16	HapMap release 22 (build 36)	none	ProbABEL, Merlin	1.02
BRIGHT	Affymetrix 500K	CHIAMO	call rate <95% (MAF>0.05) and <99% (MAF<0.05), pHWE <5.7E-7	490,032	IMPUTE	HapMap release 21 (build 35)	none	SNPTEST	1.00
CARDIA	Affymetrix 6.0	BEAGLE, Birdseed	call rate <95%, MAF<3%, pHWE <10E-4	579,630	BEAGLE	HapMap release 22 (build 36)	Rsq<0.3, MAF<1%	ProbABEL, PLINK, R	1.01
CHS	Illumina 370 CNV	Illumina BeadStudio	Call rate <97%, heterozygotes=0 , pHWE<1E-5, SNP not in HapMap	306,655	BimBam	HapMap CEU release 22 (build 36)	dosage variance < 0.01	Linear an logistic regression using R	1.01
CoLaus	Affymetrix 500K	BRLMM	call rate <70%, MAF <1%, pHWE <1E-7	390,631	IMPUTE v0.2.0	HapMap release 21 (build 35)	none	Matlab	1.02
CROATIA-KORCULA	370CNV-Quad	BeadStudio	call rate <98%, MAF <1%, pHWE <10E-6	300,233	MACH v1	HapMap release 22 (build 36)	none	ProbABEL,mmscore argument	0.98

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CROATIA-SPLIT	370CNV-Quadv3	GenomeStudio	call rate <98%, MAF <1%, pHWE <10E-6	330,889	MACH v1	HapMap release 22 (build 36)	none	ProbABEL,mmscore argument	1.01
CROATIA-VIS	HumanHap 300v1	BeadStudio	call rate <97%, MAF <1%, pHWE <10E-6	283,073	MACH v1	HapMap release 22 (build 36)	none	ProbABEL,mmscore argument	1.00
DESIR	Infinium Human1 and Hap300 BeadArrays	Illumina genome studio	call rate <95%, MAF <1%, pHWE <10E-4	300,286	IMPUTE v1	HapMap release 22 (build 36)	none	PLINK, R, SNPTEST	1.00
EPIC-Norfolk cohort	Illumina 370CNV /OmniExpress	GenomeStudio	call rate <98%, MAF<1%, pHWE <10E-6	188,473	IMPUTE v1.0	HapMap release 22 (build 36)	none	PLINK, SNPTEST	1.01
ERF	Affymetrix 500K	BRLMM	call rate <90%, MAF<1%, pHWE <10E-6	382,037	IMPUTE v0.3.1	HapMap release 21 (build 35)	none	SAS, Stata, EIGENSTRAT, PLINK	1.03
Estonian Biobank	Illumina 6k, Illumina 318K, Illumina 370K and Affymetrix 250K	Illumina BeadStudio, BRLMM	call rate <98%, MAF <1%, pHWE <10E-6	450,877	MACH v1.0.16	HapMap release 22 CEU (Build 36)	none	ProbABEL, R, adjustment for family relatedness	1.02
Family Heart Study (FamHS)	Illumina 550K, Illunina 610K, Illumina 1M	BeadStudio-gencall v3.0	MAF <1%, pHWE <1E-6	503,187	MACH v1.0.16	HapMap release 22 (build 36)	none	R	1.01
FHS	Affymetrix 500K, Affymetrix 50K supplemental	BRLMM	call rate <97%, pHWE <1E-6, Mishap p<1e-9, >100 Mendel errors, MAF<1%, strand mismatch with HapMap, not in HapMap	378,163	MACH v1.0.15	phased CEU haplotypes, HapMap release 22 (build 36)	none	kinship, GEE and GWAF packages in R gee() in GEE package in R	1.03
Health 2000	Illumina 610k	Illuminus	call rate <95%, MAF <1%, pHWE <10E-6	555,388	MACH v1.0.16	HapMap release 22 (build 36)	none	ProbABEL, PLINK, R	1.03
InCHIANTI	Illumina 550K	BeadStudio	call rate <98.5%, MAF <1%, pHWE <10E-4	484,115	MACH v1.0.16	HapMap release 22 (build 36)	none	ProbABEL, Merlin	1.02
INCIPE	Illumina,Infinium DNA Analysis Assay	Illuminus	call rate <97%, MAF <1%, pHWE <10E-5	635,654	IMPUTE v2	HapMap release 22 (build 36)	none	SNPTEST	1.00
INGI-Carlantino	Illumina 370CNV	BeadStudio	call rate <97%, MAF <1%, pHWE <10E-6	298,354	MACH	HapMap release 22 (build 36)	none	GenABEL, ProbABEL	1.00
INGI_CILENTO	370K Illumina	GenomeStudio (HumanCNV370 -Quadv3_C.egt)	call rate <95%	299,456	MACH v1.0.16	HapMap release 22 (build 36)	none	GenABEL,ProbABEL, R	0.99
INGI-FVG	Illumina 370CNV	BeadStudio	call rate <97%, MAF <1%, pHWE	306,478	MACH	HapMap release 22	none	GenABEL, ProbABEL	0.98

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			<10E-6			(build 36)			
INGI-Val Borbera	Illumina SNP array 370K - HumanCNV370-Quadv3	BeadStudio	call rate <90%, MAF<1%, pHWE <10E-4	324,319	MACH	HapMap release 22 (build 36)	none	GenABEL, ProbABEL, R	0.99
KORA F3	Affymetrix 500K	BRLMM	individual call rate <93%	355,344	IMPUTE	HapMap release 21 (build 35)	none	SNPTEST v2.1.1	1.00
KORA F4	Affymetrix 6.0	Birdseed2	individual call rate <93%	909,622	IMPUTE	HapMap release 22 (build 36)	none	SNPTEST v2.1.1	1.01
LBC1936	Illumina Human 610_Quadv1	Illumina	call rate <98%, MAF <1%, pHWE <0.001	535,709	MACH v1.0.16	HapMap release 22 (build 36)	none	mach2qtl, R	0.99
LifeLines	Illumina CytoSNP12 V2	Illumina	call rate <95%, MAF<1%, pHWE <10E-5	257,581	BEAGLE v3.1.0	HapMap release 23a CEU	info<0.1, MAF<0.01	PLINK,Stata	1.02
LOLIPOP_EW_A	Affymetrix 500K	BRLMN	call rate <=90%, MAF <1%, pHWE <=10E-6	374,773	MACH	HapMap release 21 (build 35)	none	mach2qtl	1.00
LOLIPOP_EW_P	Perlegen custom	NA	call rate <=90%, MAF <1%, pHWE <=10E-6	184,469	MACH	HapMap release 21 (build 35)	none	mach2qtl	1.01
LOLIPOP_EW610	Illumina Human 610	BeadStudio	call rate <=90%, MAF<1%, pHWE <=10E-6	544,620	MACH	HapMap release 22 (build 36)	none	mach2qtl	0.99
LURIC	Affymetrix 6.0	Birdseed	individual call rate <96%	866,316	IMPUTE v0.4.2	HapMap release 22 (build 36)	none	SNPTEST v2.1.1	1.00
MICROS	HumanHap 300v2	BeadStudio	call rate <98%, MAF <1%, pHWE <10E-6	290,356	MACH v1	HapMap release 22 (build 36)	none	ProbABEL,mmscore argument	1.00
NESDA	Perlegen 600K	Perlegen	call rate <95%, MAF 1%, 5% genotype mismatches, 5% Mendelian errors	435,291	IMPUTE v0.3.2	HapMap release 22 (build 36)	Valid p-value	SNPTEST v2.1.1, R	1.02
NSPHS	HumanHap 300v2	BeadStudio	call rate <98%, MAF<1%, pHWE <10E-6	292,220	MACH v1.0.15	HapMap release 22 (build 36)	none	ProbABEL,mmscore argument	1.00
ORCADES	most HumanHap 300v2, some 370CNV-Quad	BeadStudio	call rate <98%, MAF<1%, pHWE <10E-6	293,607	MACH v1	HapMap release 22 (build 36)	none	ProbABEL,mmscore argument	1.00
PREVEND	Illumina CytoSNP12 V2	Illumina	call rate <98%, MAF<1%, pHWE <10E-5	244,868	BEAGLE v3.1.0	HapMap release 23a CEU	info<0.1, MAF<0.01	PLINK,Stata	1.05

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PROCARDIS	Illumina 610 & Illumina 1M	GenCall (BeadStudio)	call rate <95%, MAF<1%, pHWE <1E-6	487,783	MACH v1.0.16	HapMap release 22 (build 36)	none	STATA 10	1.03
RS-I	Version 3 Illumina Infinium II HumanHap550	BeadStudio	call rate <98%, MAF<1%, pHWE <10E-5	530,683	MACH v1.0.15	HapMap release 22 (build 36)	none	ProbABEL	1.02
RS-II	Version 3 Illumina Infinium II HumanHap550	BeadStudio	call rate <98%, MAF<1%, pHWE <10E-5	495,478	MACH v1.0.15	HapMap release 22 (build 36)	none	ProbABEL	1.00
SardiNIA	Affymetrix 10K, 500K, 6.0	BRLMM (10K/500K), Birdseed (6.0)	call rate <90% (10K/500K) and <95% (6.0), MAF<5% (10K/500K) and <1% (6.0), pHWE<10E-6	731,209	MACH v1.0.10	HapMap release 22 (build 36)	rsqr<0.3, MAF <1%, Excess Mendelian Errors	Merlin (fastAssoc), R	1.05
SHIP	Affymetrix 6.0	Birdseed v2	none	869,224	IMPUTE v0.5.0	HapMap release 22 (build 36)	none	Caché, InforSense, R, QUICKTEST	1.03
SOCCS	HumanHap 300v1 and 240S	BeadStudio	call rate <98%, MAF<1%, pHWE <10E-6	512,938	MACH v1	HapMap release 22 (build 36)	none	ProbABEL	1.01
Sorbs	Affymetrix 500K Affymetrix 6.0	BRLMM Birdseed	call rate <95%, MAF<1%, pHWE <10E-4	378,513	IMPUTE v1.0.0	HapMap release 21 (build 35)	none	GenABEL, ProbABEL	1.02
TwinsUK	Illumina 317K+610K+1M	Illumina protocol	call rate <95%, MAF<1%, pHWE <10E-4	NA	IMPUTE v2	HapMap release 24 (build 36)	none	GenABEL	1.00
WGHS	Illumina HumanHap 300 DuoPlus	Illumina BeadStudio 3.3	call rate <90%, individual call rate <98%, MAF<1%, pHWE <10E-6	317,186	MACH v1.0.15	HapMap CEU release 22 (build 36)	none	SAS 9.1, ProbABEL, R, bash scripts	NA
Young Finns Study	Illumina 670k	Illuminus	call rate <95%, MAF<1%, pHWE <10E-6	546,677	MACH v1.0.16	HapMap release 22 (build 36)	none	ProbABEL, PLINK, R	1.02
Replication cohorts									
EPIC cases	Illumina 370CNV /OmniExpress	GenomeStudio	call rate <98%, MAF<1%, pHWE <10E-6	188,473	IMPUTE v1.0	HapMap release 22 (build 36)	none	PLINK, SNPTEST	
GHS I	Affymetrix 6.0	Birdseed	call rate <95%, MAF<1%, pHWE<10E-4	662,405	IMPUTE v2.1.0	HapMap release 24 (build 36)	none	MetABEL, R	
GHS II	Affymetrix 6.0	Birdseed	call rate <95%, MAF<1%, pHWE<10E-4	673,914	IMPUTE v2.1.0	HapMap release 24 (build 36)	none	MetABEL, R	

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GSK cases/controls	Illumina 550K	BeadStudio	call rate <98%, pHWE <10E-5	517,946	IMPUTE v2	HapMap3 release #2 (Feb 2009) and 1000g data freeze Mar2010	none	PLINK, R, GTOOL	
HPFS	Illumina Infinium Omni Express	BeadStudio	MAF<1%, pHWE<10E-4, genotyping rate <97%	553,716	MACH v1.0.16	HapMap release 22 (build 36)	none	ProbABEL, PLINK, R	
Hunter Community Study	Illumina 610K-Quad	Illumina	call rate <95%, MAF<1%, pHWE <10E-6	513,977	MACH v1.0.16	HapMap release 24 (build 36.1)	MAF<0.01, oevar_imp<0 .3	PLINK, SAS,R	
Lifelines replication	Illumina CytoSNP12 V2	Illumina	call rate <95%, MAF<1%, pHWE <10E-5	257,581	BEAGLE v3.1.0	HapMap rel 22 CEU	info<0.1, MAF<0.01	PLINK,Stata	
LURIC_GZ	Affy 500k	BRLMM	call rate <95%, pHWE <10E-6	393,157	MACH	1000Genomes	none	SPSS, PLINK	
LURIC_HD	Affy 6.0	Birdseed v2	call rate <95%, pHWE <10E-6	893,909	MACH	1000Genomes	none	SPSS, PLINK	
MARS cases	Illumina 100k,300k,610k	BeadStudio	chipwise: call rate <98%, pHWE < 10E-05, over all chips: call rate <98%, MAF < 1%, pHWE < 10E-05	327,336	IMPUTE v2	HapMap3 release #2 (Feb 2009) and 1000g data freeze Mar2010	none	PLINK, R, GTOOL	
NHS	Illumina Infinium Omni Express	BeadStudio	MAF<1%, pHWE<10E-4,genotyping rate <97%	553,716	MACH v1.0.16	HapMap release 22 (build 36)	none	ProbABEL, PLINK, R	
OGP-Talana	Affymetrix 500k	BRLMM	call rate <93%, MAF <1%, pHWE <10E-5	329,122	MACH v1.0.16	HapMap release 22 (build 36)	Rsq<0.3	R, GenABEL, ProbABEL	
SAPALDIA	Illumina Human610-Quad BeadChip	Gencall	only autosomal (excl. sex-chromosomal, mitochondrial)	567,589	MACH v.1.0.16	HapMap release 22 (build 36)	none	ProbABEL, PLINK, Stata	
SHIP-Trend	Illumina Omni 2.5	GenomeStudio Genotyping Module v1.0	pHWE <= 0.0001, call rate <=90%, monomorphic SNPs	1,782,967	IMPUTE v2.1.2.3	HapMap release 22 (build 36)	duplicate RSID but different positions	Caché, InforSense, R, QUICKTEST	
Samples of other ancestries									
LOLIPOP_ IA317	Illumina HumanHap300K	BeadStudio	call rate <= 90%, MAF < 1%,	245,892	MACH	HapMap release 21	none	mach2qtl	

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			pHWE <= 10E-6			(build 35)			
LOLIPOP_IA610	Illumina Human610	BeadStudio	call rate <= 90%, MAF < 1%, pHWE <= 10E-6	544,390	MACH	HapMap release 21 (build 35)	none	mach2qtl	
LOLIPOP_IA_P	Perlegen custom	Perlegen	call rate <= 90%, MAF < 1%, pHWE <= 10E-6	170,055	MACH	HapMap release 21 (build 35)	none	mach2qtl	
CARe Consortium (ARIC, CARDIA, JHS)	Affymetrix 6.0	Birdseed v1.33	all chip QC + pi_hat 0,05 for rate step	763,537 to 846,628	MACH, 2 rounds	combined CEU+YRI reference panel	MAF 1%, rsq_hat 0.3	plink --dosage	
BioBank Japan	Illumina HumanHap610-Quad Genotyping BeadChip	BEADSTUDIO-Genotyping Module v3.3.7	call rate <99%, MAF<1%, pHWE <10E-7	477,784	MACH v1.0.10	HapMap Phase II JPT+CHB individuals (release 24, build 36)	none	R v2.11.0	

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Supplementary Table 4: All SNPs Associated with Serum Urate at $p<5*10^{-8}$

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Supplementary Table 5: Results from Conditional Analyses to Test Independence

										single SNP analyses			multiple SNP analyses			
SNP	chr	bp (b36)	closest gene	known locus	p-value discovery	effect difference (mg/dl)	s.e. of effect difference	p-value difference	percent change in effect	effect (mg/dl)	s.e.	p-value	effect (mg/dl)	s.e.	p-value	n
rs1471633	1	144435096	*PDZK1*	yes	**1.40E-26**	0.002	0.010	8.3E-01	3.3	0.064	0.007	4.0E-20	0.062	0.007	9.7E-20	69861
rs11264341	1	153418117	*TRIM46*	no	**1.04E-14**	-0.003	0.011	7.6E-01	6.9	-0.047	0.008	1.0E-09	-0.044	0.007	4.6E-09	65167
rs1260326	2	27584444	*GCKR*	yes	**1.31E-40**	0.001	0.010	9.0E-01	1.8	0.068	0.007	3.7E-22	0.067	0.007	1.9E-22	69861
rs17050272	2	121022910	*INHBB*	no	**9.36E-09**	-0.003	0.012	8.2E-01	-6.6	0.041	0.008	1.0E-06	0.044	0.008	8.6E-08	65167
rs2307394	2	148432898	*ORC4L*	no	**7.26E-09**	-0.003	0.010	7.9E-01	8.2	-0.034	0.007	3.2E-06	-0.032	0.007	1.2E-05	69861
rs6770152	3	53075254	*SFMBT1*	no	**2.66E-16**	0.000	0.010	9.6E-01	1.0	-0.049	0.007	1.4E-12	-0.049	0.007	6.0E-13	69861
rs12498742	4	9553150	*SLC2A9*	yes	**1.2E-786**	0.028	0.012	**2.2E-02**	7.3	0.380	0.008	0.0E+00	0.352	0.009	0.0E+00	69861
rs6847019	4	9575347	*SLC2A9*	yes	**2.62E-53**	0.082	0.013	**6.3E-11**	**78.8**	0.104	0.008	7.3E-35	0.022	0.009	1.8E-02	69861
rs11932627	4	9765275	*WDR1*	yes	**5.59E-11**	-0.039	0.027	1.4E-01	**41.8**	-0.094	0.019	5.5E-07	-0.055	0.019	4.2E-03	69861
rs10939829	4	9909917	*ZNF518B*	yes	**4.49E-109**	-0.078	0.012	**2.7E-10**	**57.5**	-0.135	0.008	5.6E-61	-0.058	0.009	3.7E-10	69861
rs11099098	4	81388936	*FGF5*	no	7.65E-07	-0.001	0.011	9.4E-01	3.8	-0.023	0.008	4.1E-03	-0.023	0.008	4.8E-03	65167
rs2231142	4	89271347	*ABCG2*	yes	**4.43E-116**	0.001	0.017	9.6E-01	0.4	0.213	0.012	8.5E-71	0.212	0.012	4.9E-67	65167
rs17014018	4	89467059	*PPM1K*	yes	**9.69E-14**	0.086	0.025	**7.3E-04**	**90.0**	0.095	0.018	9.4E-08	0.010	0.018	6.0E-01	65167
rs17632159	5	72467238	*TMEM171*	no	**2.00E-09**	0.002	0.011	8.8E-01	-6.4	-0.025	0.008	1.4E-03	-0.027	0.008	4.9E-04	69861
rs675209	6	7047083	*RREB1*	yes	**1.38E-21**	0.004	0.011	7.1E-01	7.1	0.059	0.008	1.8E-13	0.055	0.008	2.2E-12	69861
rs969297	6	25651618	*LRRC16A*	yes	**4.86E-08**	-0.024	0.012	**4.9E-02**	**81.0**	-0.029	0.008	5.3E-04	-0.006	0.009	5.2E-01	69861
rs1165151	6	25929595	*SLC17A1*	yes	**4.52E-60**	-0.004	0.010	6.5E-01	4.8	-0.092	0.007	1.6E-40	-0.087	0.007	8.2E-37	69861
rs853679	6	28404842	*ZNF323*	yes	9.50E-07	0.020	0.015	1.7E-01	**43.9**	0.046	0.010	8.4E-06	0.026	0.010	1.3E-02	69861
rs9262499	6	31095077	*MUC21*	yes	5.96E-07	-0.010	0.010	3.3E-01	**29.9**	-0.034	0.007	4.1E-06	-0.024	0.007	1.1E-03	69861
rs729761	6	43912549	*VEGFA*	no	**3.05E-12**	-0.001	0.011	9.2E-01	2.3	-0.047	0.008	6.1E-09	-0.046	0.008	5.6E-09	69861
rs1178977	7	72494985	*BAZ1B*	no	**6.68E-12**	0.010	0.013	4.5E-01	**20.7**	0.046	0.009	3.1E-07	0.036	0.009	2.9E-05	69861
rs10480300	7	151036938	*PRKAG2*	no	9.37E-07	-0.002	0.011	8.8E-01	-6.3	0.027	0.008	4.7E-04	0.029	0.008	1.4E-04	69861
rs17786744	8	23832951	*STC1*	no	8.82E-08	0.003	0.010	8.0E-01	-10.3	-0.024	0.007	5.5E-04	-0.027	0.007	9.1E-05	69861

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rs2941484	8	76641323	*HNF4G*	no	**3.91E-17**	-0.001	0.010	9.6E-01	-1.1	0.046	0.007	7.7E-11	0.046	0.007	1.3E-11	69861
rs10813960	9	33170362	*B4GALT1*	no	7.85E-07	-0.003	0.011	8.0E-01	7.3	-0.038	0.008	1.8E-06	-0.035	0.008	5.6E-06	69861
rs10821905	10	52316099	*A1CF*	no	**3.45E-12**	-0.003	0.013	8.3E-01	-5.7	0.049	0.009	1.2E-07	0.052	0.009	9.4E-09	69861
rs1171614	10	61139544	*SLC16A9*	yes	**6.48E-23**	-0.009	0.014	5.3E-01	12.0	-0.073	0.010	7.1E-14	-0.064	0.010	5.2E-11	65167
rs2090123	10	61195573	*CCDC6*	yes	**1.26E-08**	0.017	0.011	1.1E-01	**49.9**	0.034	0.008	4.9E-06	0.017	0.008	2.2E-02	65167
rs1493664	11	25657565	*LUZP2*	no	8.27E-07	0.002	0.010	8.5E-01	-7.1	-0.027	0.007	2.1E-04	-0.029	0.007	4.3E-05	65167
rs2078267	11	64090690	*SLC22A11*	yes	**8.73E-36**	0.002	0.010	8.6E-01	-2.1	-0.087	0.007	2.6E-34	-0.089	0.007	2.9E-37	69861
rs478607	11	64234639	*NRXN2*	yes	**5.31E-10**	0.004	0.013	7.7E-01	-10.0	-0.039	0.010	4.9E-05	-0.043	0.009	4.6E-06	69861
rs642803	11	65317196	*OVOL1*	no	**4.51E-14**	-0.006	0.010	5.5E-01	16.2	-0.036	0.007	3.1E-07	-0.030	0.007	1.1E-05	69861
rs2195525	11	118740614	*USP2*	no	2.59E-07	-0.001	0.010	9.0E-01	3.3	-0.040	0.008	8.6E-08	-0.039	0.007	1.1E-07	69861
rs3741414	12	56130316	*INHBC*	yes	**9.79E-22**	0.003	0.012	7.9E-01	-4.7	-0.068	0.009	7.7E-15	-0.071	0.009	6.7E-17	69861
rs653178	12	110492139	*ATXN2*	no	**2.45E-10**	-0.001	0.010	9.5E-01	1.5	-0.039	0.007	3.3E-08	-0.038	0.007	2.2E-08	69861
rs584480	13	71243506	*DACH1*	no	2.91E-07	0.002	0.010	8.8E-01	-6.7	-0.022	0.007	1.9E-03	-0.024	0.007	6.3E-04	69861
rs10851850	15	70273563	*GRAMD2*	no	8.33E-07	-0.006	0.011	5.8E-01	**23.3**	-0.027	0.008	4.6E-04	-0.021	0.008	1.1E-02	69861
rs4777542	15	70869419	*ADPGK*	no	1.46E-07	-0.010	0.011	3.9E-01	**28.6**	-0.034	0.008	8.6E-06	-0.025	0.008	3.0E-03	65282
rs1394125	15	73946038	*UBE2Q2*	no	**9.78E-11**	0.006	0.011	5.8E-01	15.2	0.041	0.008	4.1E-07	0.035	0.008	1.0E-05	65167
rs6598541	15	97088658	*IGF1R*	no	**5.20E-13**	-0.002	0.010	8.5E-01	-5.5	0.036	0.007	9.4E-07	0.038	0.007	1.1E-07	69861
rs7193778	16	68121391	*NFAT5*	no	**2.36E-08**	-0.002	0.014	8.8E-01	4.1	-0.054	0.010	1.3E-07	-0.052	0.010	2.0E-07	69861
rs7188445	16	78292488	*MAF*	no	1.15E-07	-0.003	0.010	7.6E-01	9.1	-0.034	0.007	4.5E-06	-0.031	0.007	1.8E-05	69861
rs7224610	17	50719787	*HLF*	no	**4.74E-11**	0.002	0.010	8.6E-01	-4.3	-0.042	0.007	4.3E-09	-0.044	0.007	3.1E-10	69861
rs2079742	17	56820479	*BCAS3*	no	**6.24E-09**	0.000	0.015	9.8E-01	0.8	0.036	0.011	6.7E-04	0.035	0.010	5.5E-04	69861
rs164009	17	71795264	*QRICH2*	no	7.06E-07	-0.001	0.010	9.4E-01	-2.8	0.025	0.007	3.4E-04	0.026	0.007	1.6E-04	69861
rs1035942	19	7150803	*INSR*	no	2.24E-07	-0.001	0.011	9.6E-01	-1.9	0.031	0.008	8.6E-05	0.031	0.008	4.0E-05	69861

Horizontal lines separate different loci. Single SNP and multiple SNP analyses were performed using the same sample size (n). Legend of bold entries: SNP is bold if lead SNP of locus, thus taken forward to replication stage. P-value discovery is bold if genome-wide significant. P-values for difference between effects from single SNP and multiple SNP models are bold if nominally significant. Percent change of the difference in effect estimates between the single and the multiple SNP model compared to the single SNP model are bold if >20.
Abbreviations: s.e.: standard error; n: sample size.

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Supplementary Table 6: Separate Results from Discovery, Replication and Combined Analyses for SNP-Urate Associations

Supplementary Table 6 is provided in a separate .xlsx document.

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Supplementary Table 7: Characterization of Implicated Loci: Gene Function and Investigations in the NHGRI GWAS Catalog and a Serum Metabolite Database

Signal type	Sentinel rsID	Recombinant interval chr and start and end position (b36)[1]	Core gene[2]	Other genes in recomb. interval[3]	Core gene function	gene expression: transcript, protein[4]	Human disease mutations (OMIM database)	Associations with complex traits from the human GWAS catalog (r^2 >0.5)[5]	Metabolites associated with index SNP ($p<5*10^{-6}$)
overall	rs1471633	1 144433813 144833808	*PDZK1*	*PDZK1P1 ~~GPR89C NBPF11 GPR89A~~*	This gene encodes a PDZ domain-containing scaffolding protein; these molecules bind to and mediate the subcellular localization of target proteins. PDZK1 has been shown to interact with several members of the Solute carrier family such as SLC22A12 and SLC17A1 both of which are detected in this study. PDZK1 may be involved in the coordination of a diverse range of regulatory processes for ion transport and second messenger cascades, and in the regulation of proximal tubular Na(+)-dependent inorganic phosphate cotransport, therefore playing an important role in tubular function (By similarity).	The *PDZK1* transcript is predominantly detected in kidney and liver; expression is also detected in ovary, colon, breast, small intestine, endometrium, exocrine pancreas. Protein staining is observed in many tissues, strong in kidney and GI tract (HPA).	none	Serum uric acid (rs12129861, Kolz M et al.), Serum urate (rs1967017, Yang Q et al.)	
overall	rs11264341	1 153367551 154105051	*TRIM46*	*RAG1AP1 SCAMP3 RUSC1 MUC1 SYT11 GBAP YY1AP1 GON4L ASH1L C1orf104 HCN3 DAP3 MTX1 DPM3 GBA KRTCAP2 MSTO1 FDPS CLK2 EFNA1 (PKLR) THBS3 C1orf2*	The *TRIM46* gene product contains a motif associated with binding to microtubules[104], otherwise little is known.	*TRIM46* is transcribed around median levels in most tissues (GeneAtlas). The protein is expressed in liver (HPRD).	none	Esophageal cancer and gastric cancer (rs4072037, Abnet CC et al.), Serum magnesium levels (rs4072037, Meyer TE et al.)	
			PKLR		Encodes the liver and erythrocyte specific isozymes of the glycolytic enzyme that catalyzes conversion of phohsphoenolpyruvate and ADP to pyruvate and ATP. ATP is one of the main precursors of uric acid.	Pyruvate kinase, liver and red blood cell, is highly expressed in liver and endothelial cells, and to a lesser degree in kidney (BioGPS). The protein is found in liver and several other tissues (HPRD).	Pyruvate definiciency of erythrocytes (#266200)		
overall	rs1260326	2 27240853 27706353	*GCKR*	*TRIM54 DNAJC5G FTHL3 SLC30A3 PPM1G EIF2B4 CAD*	*GCKR* encodes a protein belonging to the GCKR subfamily of the SIS (Sugar ISomerase) family of proteins. The gene product is a regulatory protein that inhibits	The GCKR transcript is principally expressed in liver (BioGPS). Protein is found in liver and	This gene is considered a candidate susceptibility	Triglycerides (rs1260333, Waterworth DM et al.), Triglycerides-Blood Pressure (TG-BP)	

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				CCDC121 UCN FNDC4 XAB1 C2orf16 ZNF512 NRBP1 SNX17 KRTCAP3 ZNF513 C2orf28 IFT172 MPV17 GTF3C2 SLC5A6	glucokinase in liver and pancreatic islet cells by binding non-covalently to form an inactive complex with the enzyme.	pancreas.	gene for a form of maturity-onset diabetes of the young (MODY)[105]. Heterozygous inactivating GCK mutations cause hyperglycemia, whereas activating mutations cause hypoglycaemia[106].	(rs780093, Kraja AT et al.), Waist Circumference - Triglycerides (WC-TG) (rs780093, Kraja AT et al.), Crohn's disease (rs780093, Franke A et al.), Serum urate (rs780093, Yang Q et al.), Serum calcium (rs780093, O'Seaghdha CM et al.), C-reactive protein (rs1260326, Dehghan A et al.), Hypertriglyceridemia (rs1260326, Johansen CT et al.), Chronic kidney disease (rs1260326, Köttgen A et al.), Hematological and biochemical traits (rs1260326, Kamatani Y et al.), Two-hour glucose challenge (rs1260326, Saxena R et al.), Triglycerides (rs1260326, Kathiresan S et al.), Other metabolic traits (rs1260326, Sabatti C et al.), Waist circumference and related phenotypes (rs1260326, Chambers JC et al.), Fasting glucose-related traits (rs780094, Dupuis J et al.), Fasting insulin-related traits (rs780094, Dupuis J et al.), Serum uric acid (rs780094, Kolz M et al.), Triglycerides (rs780094, Aulchenko YS et al.), C-reactive protein (rs780094, Ridker PM et al.), Triglycerides (rs780094, Kathiresan S et al.), Triglycerides (rs780094, Willer CJ et al.), LDL cholesterol (rs780094, Wallace C et al.)	
overall	rs17050272	2 120770240	*INHBB*	*GLI2*	Activin B, consisting of two inhibin betaB	Transcript is found at	none		

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		121323240			(INHBB) subunits, is a hormone with effects on gonadal function, reproduction and fetal development. It may play a role in physiological energy balance and has been found to inhibit lipolysis [107,108]. Activins bind to the ACVR2A receptor, the encoding gene of which is also found in our study.	high levels in testis and prostate (BioGPS). The protein is highly detected in kidney, liver and gallbladder (HPA).			
overall	rs2307394	2 148171238 148676238	*ORC4L*	*(ACVR2A) MBD5*	The origin recognition complex subunit 4 gene (*ORC4L*) encodes a subunit of a complex necessary for DNA replication.	The transcript as well as the protein is found ubiquitously (BioGPS and HPRD).	none		
			ACVR2A		The *ACVR2A* gene encodes an activin A type II receptor, which has protein kinase activity. Type I and II receptors form a complex; type II is required for ligand binding. ACVR2A can bind activin A, B (encoded by *INHBB* and also found in our screen) or AB as well as inhibin A (UniProt, STRING) at high affinity. There is a HNF-1A transcription factor, also found in our screen, binding site in the *ACVR2A* gene promoter (GeneCards). The associated SNP, rs2307394, is an eQTL for the *ACVR2A* transcript in several tissues (Supplementary Table 14).	The *ACVR2A* transcript is expressed around median levels in most tissues (BioGPS).	none		
overall	rs6770152	3 52805000 53152000	*SFMBT1*	*RFT1 (MUSTN1) ITIH4 ITIH3 TMEM110*	*SFMBT1* shares high similarity with the Drosophila Scm (sex comb on midleg) gene. It encodes a protein which contains four malignant brain tumor repeat (mbt) domains and may be involved in antigen recognition. Several alternative splice variants that encode the same protein have been characterized [provided by RefSeq].	The *SFMBT1* transcript is expressed in most tissues around the median level, with substantially higher expression in testis. Staining is strong in hematopoietic, liver and pancreas, lung, GI tract, female and male tissues, urinary tract and endocrine tissues (HPA). Protein is found ubiquitously (HPRD).	none		
			MUSTN1		*MUSTN1* encodes the musculoskeletal, embryonic nuclear protein 1, which may be involved in the development and regeneration of the musculoskeletal system [Uniprot]. Evidence supports a role of the MUSTN1 transcript in the regulation of chondrocyte function in vitro[109] and in vivo[110].	No expression data is available for the MUSTN1 transcript. Protein is found in many diverse tissues (HPRD).	none		
overall	rs12498742	4 9523329 10025829	*SLC2A9*	*~~WDR1~~*	*SLC2A9* encodes GLUT9, a high-affinity urate transporter involved in renal urate reabsorption[111,112]. Two isoforms encoded	The *SLC2A9* transcript is expressed in most tissues around the	Renal hypouricemia (MIM	Serum urate (rs16890979, Dehghan A et al.), Serum uric acid	urate (p=1.6E-17)

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					by different transcript variants have been described: one encoding for a transporter responsible for transporting urate from tubular cells to the peritubular interstitium following the uptake of urate from the luminal space by *SLC22A12*[113], and the other encoding a transporter responsible for urate uptake from the luminal space into the tubular cells.	median level, with higher levels of expression in kidney (~2 fold) and CD33 myeloid cells (~4 fold). Protein is found in articular cartilage, brain, chondrocyte, colon, heart, kidney, leukocyte, liver, lung, ovary, placenta, prostate, skeletal muscle, and testis (HPRD).	#612076)[113,114].	(rs16890979, McArdle PF et al.), Serum urate (rs13129697, Yang Q et al.), Biochemical measures (rs13129697, Zemunik T et al.), Serum urate (rs737267, Vitart V et al.), Serum uric acid (rs734553, Kolz M et al.), Serum urate (rs6855911, Li S et al.), Serum uric acid (rs3775948, Charles BA et al.), Serum urate (rs7442295, Döring A et al.), Serum urate (rs7442295, Wallace C et al.)	
overall	rs11099098	4 81375845 81427845	*FGF5*		The protein encoded by this gene is a member of the fibroblast growth factor (FGF) family. FGF family members possess broad mitogenic and cell survival activities, and are involved in a variety of biological processes, including embryonic development, cell growth, morphogenesis, tissue repair, tumor growth and invasion. This gene was identified as an oncogene, which confers transforming potential when transfected into mammalian cells.	The *FGF5* transcript is expressed in most tissues around the median level. Protein cytoplasmic immunoreactivity is moderate in most normal tissues. Strong cytoplasmic staining was observed in placenta, thyroid gland and pyramidal neurons.	none	Diastolic blood pressure (rs16998073, Newton-Cheh C et al.)	
overall	rs2231142	4 89179845 89283345	*ABCG2*	*~~PKD2~~*	The gene encodes an ABC transporter, ABCG2. ABCG2 transports drugs such as chemotherapeutics. It has been shown to operate as an urate transporter, which contributes to urate excretion via the kidney. The rs2231142 variant encodes the Q141K mutation, a partial loss-of-function variant that increases susceptibility for hyperuricemia and gout[115,116].	The transcript is highly expressed in placenta and small intestine (Gene Atlas); the protein localizes to the plasma membrane of multiple tissues (HPRD).	Blood group Junior(a-) (MIM #614490)	Serum uric acid (rs2231142, Kolz M et al.), Serum urate (rs2231142, Dehghan A et al.), Serum urate (rs2199936, Yang Q et al.)	
overall	rs17632159	5 72460000 72500500	*TMEM171*	*TMEM174*	*TMEM171* encodes for an as yet uncharacterized transmembrane protein. The related *TMEM174* which is in the same LD interval is highly expressed in kidney tissue and has been proposed to enhance the activity of AP1, a transcription factor induced by a broad range of signals including stress and growth factors[117].	The *TMEM171* protein is expressed in most tissues around the median level, with higher levels of expression in thyroid. Staining was strong in lung and female tissue (HPA).	none		
overall	rs675209	6 6933500 7213000	*RREB1*		The protein encoded by *RREB1* is a zinc finger transcription factor that binds to RAS-responsive elements (RREs) of gene	The *RREB1* transcript is expressed in most tissues around the	none	Age-related macular degeneration (rs11755724, Neale BM	

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					promoters. It has been shown that RREB1 increases expression of calcitonin, which may be involved in Ras/Raf-mediated cell differentiation; it increases transcription of the angiotensinogen gene. Multiple transcript variants encoding several different isoforms have been found for this gene [provided by RefSeq].	median level. Staining was strong in CNS (brain), Hematopoietic (blood), Liver and pancreas, Digestive (GI-tract), Respiratory (lung), Cardiovascular, Female tissues, Placenta, Male tissues, Urinary tract (kidney), Skin and soft tissues and Endocrine tissues (HPA). Expression is ubiquitous (HPRD).		et al.), Serum urate (rs675209, Yang Q et al.)	
overall	rs1165151	6 25792500 26250500	*SLC17A1*	~~*HIST1H3C*~~ ~~*TRIM38*~~ ~~*HIST1H4C*~~ ~~*HIST1H2AA*~~ ~~*HIST1H4B*~~ ~~*HIST1H1A*~~ ~~*HIST1H4A*~~ ~~*HIST1H1C HFE*~~ ~~*HIST1H3B*~~ ~~*HIST1H2AC*~~ *(SLC17A3)* ~~*SCGN*~~ ~~*HIST1H2BB*~~ ~~*HIST1H1T*~~ *SLC17A4* *SLC17A2* ~~*HIST1H2BA*~~ ~~*HIST1H3A*~~ ~~*HIST1H2AB*~~ ~~*HIST1H2BC*~~	*SLC17A1* encodes a member of the SLC17/type I phosphate transporter family based on ability to cotransport sodium (Na+) and inorganic phosphate (Pi) in oocytes and believed to play an important role in phosphate homeostasis[118]. The primary function of members of this family has been shifted to diverse organic anions transport[119]. Detailed characterization of the transport properties of SLC17A1 demonstrates it to be a voltage dependent multispecific renal anion exporter able of transporting urate and likely to be involved in urate excretion under physiological condition[120].	SLC17A1 mRNA transcripts have been detected in kidney, liver and brain[118] with strong expression in the kidney cortex where protein immunodetection, in rabbit, is restricted to the brush border membranes of proximal tubules[121].		Serum uric acid (rs1183201, Kolz M et al.), Serum urate (rs1165205, Dehghan A et al.), Serum urate (rs1165196, Yang Q et al.)	
			SLC17A3		Paralog of *SLC17A1* believed to have similar function.	The mRNA is expressed predominantly in the kidney. Strong immunodectection was observed in smooth muscle cells, luminal membranes of renal tubules, basal cells of airways and squamous epithelia (HPA).	Glycogen storage disease (MIM #232240), but causality not proven.		
overall	rs729761	6 43661000 44190000	*VEGFA*	*MRPS18A* *MRPL14* *POLH* *C6orf206* *MAD2L1BP* *GTPBP2*	*VEGFA* is a member of the platelet-derived growth factor (PDGF)/vascular endothelial growth factor (VEGF) family and encodes a protein that is often found as a disulfide linked homodimer. VEGF binds to and activates a receptor tyrosine kinase, VEGFR (FLT1/VEGFR1 and KDR/VEGFR2). Vascular	The *VEGFA* transcript is expressed in most tissues around the median level and predominantly detected in prostate, lung, thyroid and pancreatic	Microvascular complications of diabetes (MIM #603933)	Chronic kidney disease (rs881858, Köttgen A et al.), Type 2 diabetes (rs9472138, Zeggini E et al.)	gamma-glutamylglutamate / pyroglutamylglycine (p=4.2E-7)

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					endothelial growth factor is a signaling protein that specifically acts on endothelial cells and has various effects, including mediating increased vascular permeability, inducing angiogenesis, vasculogenesis and endothelial cell growth, promoting cell migration, and inhibiting apoptosis.	islets. Essentially all normal tissues except lymphoid tissues displayed strong cytoplasmic staining. The positivity was often accentuated to the plasma or nuclear membrane.			
overall	rs1178977	7 72446285 72700785	*BAZ1B*	*BCL7B (MLXIPL) FZD9 TBL2*	Bromodomain adjacent to zinc finger domain, 1B: this gene encodes a member of the bromodomain protein family. The bromodomain is a structural motif characteristic of proteins involved in chromatin-dependent regulation of transcription. This gene is deleted in Williams-Beuren syndrome, a developmental disorder caused by deletion of multiple genes at 7q11.23 [provided by RefSeq].	Expression if the *BAZ1B* transcript occurs at approximately the median level for most tissues, with higher expression levels in skeletal muscle. Protein is found in Aorta, Brain, Colon, Fetus, Heart, Kidney, Leukocyte, Liver, Lung, Ovary, Pancreas, Placenta, Prostate, Skeletal muscle, Small intestine, Spleen, T Cell, Testis (HPRD). Staining is strong in brain, GI tract and male tissues (HPA).	Williams-Beuren syndrome (MIM #194050)	Plasma levels of Protein C (rs17145713, Tang W et al.), Hypertriglyceridemia (rs714052, Johansen CT et al.), Triglycerides (rs714052, Kathiresan S et al.), Caffeine consumption (rs2240466, Cornelis MC et al.), Triglycerides (rs2240466, Aulchenko YS et al.), Triglycerides (rs17145738, Kathiresan S et al.), Triglycerides (rs17145738, Willer CJ et al.), Triglycerides (rs1178979, Waterworth DM et al.), C-reactive protein (rs13233571, Dehghan A et al.)	
			MLXIPL		*MLXIPL* encodes a basic helix-loop-helix leucine zipper transcription factor of the Myc/Max/Mad superfamily. This protein forms a heterodimeric complex and binds and activates, in a glucose-dependent manner, carbohydrate response element (ChoRE) motifs in the promoters of triglyceride synthesis genes. The gene is deleted in Williams-Beuren syndrome, a multisystem developmental disorder caused by the deletion of contiguous genes at chromosome 7q11.23 [provided by RefSeq].	Expression of the *MLXIPL* transcript occurs at approximately the median level for most tissues, with higher expression levels in neural and adrenal tissue. Protein is found in Fetus, Kidney, Liver, Spleen (HPRD).	Williams-Beuren syndrome (MIM #194050)		
overall	rs10480300	7 151022285 151142785	*PRKAG2*		The gene encodes for the 5'-AMP-activated protein kinase (AMPK) subunit gamma-2. AMPK is an enzyme that regulates key enzymes for glucose metabolism and the biosynthesis of fatty acid and cholesterol (RefSeq). AMPK is involved in the regulation of endothelial function by VEGFA, a newly identified urate QTL. AMPK	The transcript and protein are ubiquitously expressed (Gene Atlas, HPRD).	familial hypertrophic cardiomyopathy-6 (MIM #600858), Wolff-Parkinson-White	Hematocrit (rs10224002, Ganesh SK et al.), Hemoglobin (rs10224002, Ganesh SK et al.)	

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					is also considered to be a redox sensor[122].		syndrome (MIM #194200), glycogen storage disease of the heart (MIM #261740)		
overall	rs17786744	8 23751500 23845500	*STC1*		Stanniocalcin 1 is a secreted homodimer that may have autocrine or paracrine function. It is synthesized in human kidney and a role in the regulation of intestinal and renal calcium and phosphate transport has been described[123].	The transcript is highly expressed in smooth muscle (Gene Atlas) The protein is expressed in many tissues (HPA).	none	Chronic kidney disease (rs10109414, Köttgen A et al.)	
overall	rs2941484	8 76603500 76727500	*HNF4G*		Hepatocyte nuclear factor 4, gamma (*HNF4G*) functions as a transcription factor. In one study, *HNF4G* knock-out mice had lowered energy expenditure and locomotor activity resulting in higher body weight[124].	Expression of the *HNF4G* transcript occurs in most tissues around the median level. Protein found in Colon, Kidney, Pancreas, Small intestine, Testis (HPRD). Strong staining in blood, liver, pancreas, GI tract, lung, female and male tissues, kidney, endocrine tissue and skin/soft tissues (HPA).	none		
overall	rs10813960	9 33098500 33178500	*B4GALT1*		Beta-1,4-galactosyltransferase 1. *B4GALT1* is one of seven beta-1,4-galactosyltransferase (beta4GalT) genes. They encode type II membrane-bound glycoproteins that appear to have exclusive specificity for the donor substrate UDP-galactose; all transfer galactose in a beta1,4 linkage to similar acceptor sugars: GlcNAc, Glc, and Xyl. This gene is unique among the beta4GalT genes because it encodes an enzyme that participates both in glycoconjugate and lactose biosynthesis [provided by RefSeq].	Expression of the *B4GALT1* transcript occurs in most tissues around the median level, with higher levels of expression in skeletal muscle. Protein found in Lacrimal gland, Liver, Placenta, Semen, Tears (HPRD). High levels of annotated protein expression occur in CNS, Hematopoietic, Liver and pancreas, GI-tract, Respiratory, Cardiovascular, Male and Female tissues, Placenta, Kidney, Skin and Endocrine tissues (HPA).	Congenital disorder of glycosilation, type IId (MIM #607091).		
overall	rs10821905	10 52114500	*A1CF*	*(ASAH2)*	APOBEC1 complementation factor. It has	Expression of the *A1CF*	none		

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		52319000		*ASAH2B*	been proposed that this complementation factor functions as an RNA-binding subunit and docks APOBEC-1 to deaminate the upstream cytidine. Studies suggest that the protein may also be involved in other RNA editing or RNA processing events. Several transcript variants encoding a few different isoforms have been found for this gene [provided by RefSeq].	transcript occurs in most tissues around the median level, with higher levels of expression in liver, pancreas and small intestine. Staining is strong in liver, pancreas, GI tract and kidney (HPA). Protein is found in Liver and Small intestine (HPRD).			
			ASAH2		Encodes the enzyme neutral ceramidasse which hydrolyzes the sphingolipid ceramide into sphingosine and free fatty acid. It is probably involved in the digestion of dietary sphingolipids in intestine by acting as a key enzyme for the catabolism of dietary sphingolipids, thereby regulating the levels of bioactive sphingolipid metabolites in the intestinal tract [UniProt].	No expression data is available in HPA (Human Protein Atlas) for this gene.	none		
overall	rs1171614	10 61057000 61142000	*SLC16A9*		Solute carrier family 16, member 9 (monocarboxylic acid transporter 9). Identified in prior GWAS of urate[125] and recently shown to be a carnitine efflux transporter[126]. L-carnitine increases the rate of fatty acid transport in mitochondria and the oxidation of pyruvate. It accelerates gluconeogenesis from propionate in rat kidney cortex[127].	Expression of the *SLC16A9* transcript is predominantly found in neural, kidney and adrenal tissue. No protein expression data in HPRD.	none	Serum uric acid (rs12356193, Kolz M et al.)	
overall	rs1493664	11 25400000 26026500	*LUZP2*		Leucine zipper protein 2.	Expression of the *LUZP2* transcript occurs in most tissues around the median level. Protein found in urine (HPRD).	none		
overall	rs2078267	11 63978500 64105500	*SLC22A11*		Solute carrier family 22 (organic anion/urate transporter), member 11. The protein encoded by *SLC22A11* is involved in the sodium-independent transport and excretion of organic anions, some of which are potentially toxic. The encoded protein is an integral membrane protein and is found mainly in the kidney and in the placenta, where it may act to prevent potentially harmful organic anions from reaching the fetus [provided by RefSeq]. Identified in prior GWAS[125,128].	The *SLC22A11* transcript is expressed in most tissues around the median level, with substantially higher levels of expression in kidney and placenta. Staining was strong in GI tract, kidney and placenta (HPA). Protein is found in kidney and placenta (HPRD).	none	Serum urate (rs2078267, Yang Q et al.), Serum uric acid (rs17300741, Kolz M et al.)	
overall	rs478607	11 64105500 64343000	*NRXN2*	*SF1 (SLC22A12) RASGRP2 MAP4K2 PYGM*	Encodes a member of the neurexin family of neuronal cell surface proteins that function as cell adhesion molecules during	Alternative splicing and the use of alternative promoters may			

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				MEN1	synaptogenesis and in intercellular signaling.	generate thousands of transcript variants[129]. mRNA expression predominantly in brain and neural tissues with strong expression in the cerebellum.			
			SLC22A12		Encodes for URAT1, a high-affinity urate anion exchanger that was the first urate transporter characterized[130]. URAT1's localization on the brush membrane of renal proximal tubules, its interaction with various uricosuric drugs and the higher fractional excretion of urate in individuals with URAT1 loss of function mutations are in agreement with a role in renal urate reabsorption, in exchange of organic anions.	The intestinal tract showed weak to moderate cytoplasmic URAT1 protein immunodetection while a subset of cells in renal tubules exhibited strong membranous immunoreactivity. Remaining normal cells were generally negative (HPA).	Idiopathic renal hypouricemia (MIM #220150)		
overall	rs642803	11 65016000 65326500	*OVOL1*	*(LTBP3) PCNXL3 HTATIP DKFZp761E198 MAP3K11 RNASEH2C EHBP1L1 MALAT1 KCNK7 SSSCA1 SCYL1 FAM89B RELA SIPA1*	*OVOL1* functions as a zinc finger transcriptional repressor. Its function in humans in unknown. OVOL1 -/- mice show growth retardation, aberrant hairs, hypogenitalism and kidney abnormalities such as cysts[131].	The transcript is expressed around the median level in most tissues (BioGPS). The protein is detected at high levels in CNS, GI tract, and reproductive tissues (HPA).	none		
			LTBP3		The protein encoded by *LTBP3* belongs to the family of latent transforming growth factor (TGF)-beta binding proteins (LTBP), which are extracellular matrix proteins with multi-domain structure. This protein is the largest member of the LTBP family possessing unique regions and with most similarity to the fibrillins. It has thus been suggested that it may have multiple functions: as a member of the TGF-beta latent complex, as a structural component of microfibrils, and a role in cell adhesion.	The *LTBP3* transcript is expressed in heart, muscle, ovaries, and prostate (HPRD).	Selective tooth agenesis (MIM #613097)		
overall	rs2195525	11 118720500 118760500	*USP2*	*(MFRP)*	The *USP2* gene encodes an ubiquitin carboxyl-terminal hydrolase 2 enzyme. Ubiquitin, a highly conserved protein involved in the regulation of intracellular protein breakdown, cell cycle regulation, and stress response, is released from degraded proteins by disassembly of the polyubiquitin chains. The disassembly process is mediated by ubiquitin-specific	The transcript is expressed around the median level in most tissues (BioGPS). Protein is ubiquitously expressed.	none		

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					proteases (USPs).				
			MFRP		*MFRP* encodes a member of the frizzled-related proteins[132]. The encoded protein may play a role in eye development.	The *MFRP* transcript is expressed around the median level in most tissues (BioGPS). Renal tubules show strong luminal membranous and cytoplasmic positivity for the protein staining. Other normal tissues are negative.	Mutations in this gene have been associated with nanophthalmos[133,134] (MIM #609549), posterior microphthalmia (MIM #611040), retinitis pigmentosa, foveoschisis, and optic disc drusen[135].		
overall	rs3741414	12 55835500 56140000	*INHBC*	*R3HDM2 NDUFA4L2 SHMT2 STAC3 NXPH4 (INHBE) LRP1*	Encodes the beta C chain of inhibin[136] which belongs to the TGF-beta superfamily. Forms activin heterodimers with the inhibin beta A or beta B (*INHBB*) chains and interacts with the activin A receptor type IIA (*ACVR2A*), both of which are detected in this study. Activins play a role in regulating the secretion of various hormones, in cell growth and differentiation, and in insulin secretion.	*INHBC* transcripts are detected ubiquitously (bioGPS).	none	Serum urate (rs1106766, Yang Q et al.)	
			INHBE		The inhibin beta E chain, the gene product of *INHBE*, is secreted as a activin homodimer in mammalian cells[137].	The transcript is highly expressed in liver (BioGPS).	none		
overall	rs653178	12 110322163 111513663	*ATXN2*	*TMEM116 SH2B3 C12orf30 RPL6 ERP29 TRAFD1 (PTPN11) ACAD10 BRAP MAPKAPK5 C12orf51 ALDH2*	The *ATXN2* gene encodes the ataxin-2 protein, containing a polyglutamine tract. Trinucleotide expansions (CAG repeat) in the coding region of this gene cause SCA2, spinocerebellar ataxia type 2.	The *ATXN2* transcript is expressed around the median level in most tissues. The protein shows cytoplasmic expression, predominately in the CNS and placenta.	Long expansions of the polyglutamine tract (greater than 33 repeats) result in spinocerebellar ataxia-2 (SCA2) an autosomal dominant form of olivopontocerebellar	Hematocrit (rs11065987, Ganesh SK et al.), Hemoglobin (rs11065987, Ganesh SK et al.), Coronary heart disease (rs3184504, Schunkert H et al.), Rheumatoid arthritis (rs3184504, Stahl EA et al.), Type 1 diabetes (rs3184504, Barrett JC et al.), Diastolic blood pressure (rs3184504, Levy D et al.), Systolic blood pressure (rs3184504, Levy D et al.), Plasma eosinophil count	gamma-glutamyl-leucine / valine (p=4.1E-8), gamma-glutamyl-leucine / glucose (p=8.0E-7)

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							atrophy Intermediate-length expansions (27-33 glutamines) contribute to susceptibility to amyotrophic lateral sclerosis (ALS) (MIM ID #183090).	(rs3184504, Gudbjartsson DF et al.), Retinal vascular caliber (rs10774625, Ikram MK et al.), Celiac disease and Rheumatoid arthritis (rs653178, Zhernakova A et al.), Chronic kidney disease (rs653178, Köttgen A et al.), Celiac disease (rs653178, Dubois PC et al.), Diastolic blood pressure (rs653178, Newton-Cheh C et al.), Celiac disease (rs653178, Hunt KA et al.)	
			PTPN11		The protein encoded by this gene is a member of the protein tyrosine phosphatase (PTP) family. This PTP contains two tandem Src homology-2 domains, which function as phospho-tyrosine binding domains and mediate the interaction of this PTP with its substrates. This protein plays a regulatory role in various cell signaling events that are important for a diversity of cell functions, such as mitogenic activation, metabolic control, transcription regulation, and cell migration.	The *PTPN11* transcript is widely expressed in most tissues. Moderate to strong protein staining was observed in the cytoplasm in most normal tissues. Additional nuclear staining was observed in respiratory epithelia, thyroid and gall bladder.	Mutations in this gene are a cause of Noonan syndrome (MIM #163950) and Leopard syndrome (MIM #151100). Defects in the *PTPN11* gene are also present in Juvenile myelomonocytic leukemia (MIM #607785)		
overall	rs584480	13 71228000 71308500	*DACH1*		The Dachshund homolog 1 (Drosophila) gene encodes a nuclear factor that together with other DNA-binding transcription factors regulates gene expression during development. SNPs in the gene associate with glomerular filtration rate.	The transcript shows low levels in all tissues except the pineal gland (BioGPS). The protein localizes to the nucleus in many cells types, including kidney, GI tract and liver (HPA).	none	Chronic kidney disease (rs626277, Köttgen A et al.)	
overall	rs4777542	15 70688500 70938500	*ADPGK*	*GOLGA6B BBS4*	ADPGK is an enzyme that catalyzes the ADP-dependent phosphorylation of glucose to glucose-6-phosphate and may play a role in glycolysis, possibly during ischemic	The *ADPGK* transcript is ubiquitously expressed. No staining info in HPA.	none		

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					conditions[138].				
overall	rs1394125	15 73917000 74185500	*UBE2Q2*	*FBXO22 (NRG4) C15orf27*	Encodes for member 2 of the ubiquitin-conjugating enzyme E2Q family. Interaction with several actin and actin-binding proteins led to the hypothesis that it plays a role in cytoskeleton structure and/or regulation[139].	Transcripts are ubiquituously expressed at low level and overexpressed in hypopharyngeal tumors.	none	Chronic kidney disease (rs1394125, Köttgen A et al.)	
			NRG4		Encodes for a member of the neuregulin family. Neuregulins activate type-1 growth factor receptors (e.g EGFR; MIM 131550) to initiate cell-to-cell signaling through tyrosine phosphorylation[140].	Transcripts are ubiquituously expressed around a low median level; protein detection is weak to moderate in many normal tissues and strong in astrocytes.	none		
overall	rs6598541	15 97062000 97139500	*IGF1R*		The encoded alpha and beta subunits interact to form a transmembrane tyrosine kinase receptor and are 60% similar to INSR subunits but with different ligand specificity and affinity. Activated upon binding of insulin like growth factor 1, IGF1R transduces an anti-apoptotic signal enhancing cell survival and plays a central role in cell cycle progression and transformation. IGF1 signaling pathway is thought to modulate human life span[141]. Beta cell-specific igf1r knock-out in mice displayed defective glucose stimulated insulin secretion and impaired glucose tolerance.	Transcript signals are ubiquitous but strongest in breast, prostate glands, ovary, colon, saphenous vein, kidney, pancreas and lower than average in liver (BioGPS). All normal tissues tested displayed moderate to strong granular cytoplasmic immunoreactivity (HPA).	Resistance to insulin-like growth factor 1 (MIM #270450)		
overall	rs7193778	16 68094500 69196000	*NFAT5*	*SF3B3 PDPR EXOSC6 LOC348174 ST3GAL2 MGC34761 COG4 NQO1 NOB1 DDX19B AARS FUK WWP2 DDX19A SNORD111 SNORD111B*	Nuclear factor of activated T-cells 5 encodes a transcription factor that regulates the expression of genes induced by osmotic stress. It upregulates the expression of several genes, among them aldose reductase that is involved in the production of organic osmolytes, most importantly sorbitol from glucose as well as the sodium/myo-inositol cotransporter (SMIT) and the sodium/chloride/betaine cotransporter[142]. The compound FK366 significantly inhibits aldose reductase which was paralleled by significant decreases of serum urate and increases in urinary urate excretion[143]. NFAT5-deficient mice show renal atrophy[144].	The transcript is expressed ubiquitously (BioGPS).	none		
overall	rs7188445	16 78252500 78315500	*MAF*	*LOC440389*	The protein encoded by *MAF* is a transcription factor. It regulates embryonic lens development and is required for normal chondrocyte differentiation in	*MAF* is highly expressed in small intestine (BioGPS). The protein is expressed in the	Juvenile-onset pulverulent cataract,	Thyroid volume and goiter risk (rs17767419, R^2=0.97, Teumer A et al.)	

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					mice[145]. rs7188445 is located within a region of 10.7 kb immediately downstream of the formerly predicted gene LOC440389 on 16q23 (78312710..78361930) that has been removed from the NCBI database as a result of the standard genome annotation processing. However, the presence of the correctly spliced mature *LOC440389* mRNA as predicted by the deleted data base entry was recently demonstrated in thyroid tissue and its withdrawal from the NCBI data base was therefore incorrect. The *LOC440389* region was shown to be associated with thyroid volume and goiter risk[146].	nucleus of most tissues. *LOC440389* is highly expressed in thyroid tissue and also expressed in skeletal muscle tissue[146].	congenital cerulean cataract-4 (MIM #610202)		
overall	rs7224610	17 50704000 50766500	*HLF*		The hepatic leukemia factor gene encodes a member of the proline and acidic-rich (PAR) transcription factor family. There is a *HNF1A* binding site in the *HLF* gene promoter.	The transcript is expressed at high levels in brain tissues (BioGPS) but also found in other tissues such as kidney, liver and thyroid (COXPRESdb).	none		
overall	rs2079742	17 56785500 56854500	*BCAS3*	*TBX2 (C17orf82)*	This gene of unknown function is overexpressed in breast cancer. *BCAS3* expression is activated by metastasis-associated protein 1 (MAT1)[147].	Generalized low expression levels (BioGPS). Transcript level higher in small intestine, lymph nodes and breast (COXPRESdb),	none	Chronic kidney disease (rs9895661, Köttgen A et al.)	
			C17orf82		Not known.	Not known.	none		
overall	rs164009	17 71771500 71827500	*QRICH2*	*(PRPSAP1) FAM100B*	Nearly no information on this gene	Generalized low expression level (BioGPS)	none		
			PRPSAP1		Phosphoribosyl pyrophosphate synthetase-associated protein 1 (PRPSAP1) encodes PAP39[148] a subunit of phosphoribosylpyrophosphate (PRPP) synthetase that is involved in urate production. No disease has been associated with this gene so far. However, mutations in PRPS1 (MIM #311850), encoding PRPP synthetase I, lead to urate overproduction[149].	Generalized high expression level. Transcript level is higher in testis, thyroid, central nervous system, lung and liver (BioGPS).	none		
overall	rs1035942	19 7108000 7201000	*INSR*		Encoded alpha and beta subunits that interact to form an insulin receptor, a transmembrane tyrosine kinase activated upon binding to insulin. It mediates glucose uptake and metabolism.	*INSR* transcript level is higher in the kidney, adrenal cortex, the pancreas as well as placenta and ovary tissues (BioGPS). Glandular cells of the gastrointestinal tract,			

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						fallopian tube, breast, renal tubules, salivary glands and exocrine pancreas showed moderate to strong cytoplasmic and membranous protein immunodetection while other tissues were negative (HPA).			
women	rs11954519	5 39526000 40469500	*DAB2*		The encoded disabled-2 protein is an intracellular adaptor protein with a proposed role in endocytosis. DAB2 binds to megalin, which is important in the reabsorption of filtered proteins by the kidney[150].	The transcript is highly expressed in placenta, followed by kidney and smooth muscle (BioGPS). The protein is detected at high levels in placenta and renal tubules (GPA).	none		
women	rs456867	5 55548500 56114000	*ANKRD55*		Ankyrin repeat domain 55 (*ANKRD55*) encodes a protein whose function is currently unknown. The superfamily ankyrin repeat domain proteins represents one class of repeat proteins, which are nonglobular proteins, playing a key role in protein-protein interactions and hence in many key physiological processes[151].	Generalized medium expression level. Transcript mainly expressed in kidney, liver, ovary, uterus, peripheral blood and testes (BioGPS).	none		
men	rs11757159	6 32447500 32790500	*HLA-DRB5*	*(C6orf10) HLA-DQB1 BTNL2 HLA-DQA1 HLA-DRB1 HLA-DQA1 HLA-DRA HLA-DQB1 HLA-DRB6 HLA-DRA*	Human major histocompatibility complex (HLA), class II, DR beta 5 determines class II molecules essential in immune response by presenting peptides derived from extracellular proteins. HLA-DRB5*1501 has been associated with multiple sclerosis[152].	Transcript mainly expressed in white blood cells (BioGPS).	none	Rheumatoid arthritis (rs9268853, Eleftherohorinou H et al.), Ulcerative colitis (rs9268853, Anderson CA et al.), Ulcerative colitis (rs9268877, Barrett JC et al.), Ulcerative colitis (rs9268877, Franke A et al.), Ulcerative colitis (rs9268923, Franke A et al.), Ulcerative colitis (rs9268480, Asano K et al.), Ulcerative colitis (rs2395185, Asano K et al.), Ulcerative colitis (rs2395185, Silverberg MS et al.), Vitiligo (rs3806156, Jin Y et al.), Type 1 diabetes (rs9272346, Cooper JD et al.), Type 1 diabetes (rs9272346, WTCCC et al.), Hepatocellular	

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								carcinoma (rs9275572, Kumar V et al.), Alopecia areata (rs9275572, Petukhova L et al.)	
			C6orf10		Little is known on the gene, but it is located in the HLA Region and has come up in several genetic association studies of auto-immune disorders[153-155].	Transcript is expressed at median levels in most tissues (BioGPS).	none		
women	rs1933737	6 116288500 116811500	*FRK*	*TSPYL1 NT5DC1 (COL10A1) TSPYL4 DSE*	Fyn-related kinase (*FRK*) encodes a tyrosine kinase that may function during G1 and S phase of the cell cycle and suppress growth. The encoded protein influences PTEN protein stability. This gene may be involved in tumor suppression.	Generalized low expression level (BioGPS). Transcript expressed mainly in cervix, uterus, lung and kidney (COXPRESDb).	none		
			COL10A1		Collagen, type X, alpha 1 (*COL10A1*) encodes a short-chain minor collagen of cartilage, expressed by hypertrophic chondrocytes during endochondral ossification. Mutations leading to altered function and synthesis of type X collagen cause heritable forms of chondrodysplasia[156]. Osteoarthritis in humans is associated with downregulation of *COL10A1* expression[157].	Generalized medium expression level (BioGPS). Transcript expressed in most tissues (COXPRESdb).	Schmid metaphyseal chondrodysplasia (MIM #156500), characterized by bone irregularities of the extremities resulting in bowlegs and coxa vara.		
women	rs2244608	12 119864663 119975163	*HNF1A*	*C12orf43 OASL*	Hepatocyte nuclear factor 1 homeobox A, transcription factor first characterized as required for the expression of several liver-specific genes[158] and that plays a role in hormone secretion, bile production, lipids and glucose metabolism. Recently shown to be a master regulator of plasma protein fucosylation[159]. Renal phenotype of mice lacking *HNF1a* included defects in renal proximal tubule reabsorption in tune with reduced levels of *SLC5A2*, *SLC17A1* and *SLC17A3* genes' expression[160], these two later transporters are also candidates in our study.	The transcript is expressed in most tissues around median level (BioGPS). Protein immuno-staining in the nucleus is the strongest in gastrointestinal tract cells, gall bladder and cells in renal tubuli (HPA). Purkinje cells also showed moderate cytoplasmic and nuclear immuno-staining while remaining normal tissues were weakly stained or negative (HPA).	Defects in this gene are a cause of maturity onset diabetes of the young type 3 (MODY3, MIM #600490)	N-glycan levels (rs7953249, Lauc G et al.), LDL cholesterol (rs2650000, Kathiresan S et al.), Other metabolic traits (rs2650000, Sabatti C et al.), C-reactive protein (rs1183910, Dehghan A et al.), C-reactive protein (rs1183910, Elliott P et al.), C-reactive protein (rs7310409, Okada Y et al.), C-reactive protein (rs7310409, Ridker PM et al.)	
women	rs12955983	18 55629500 56316000	*MC4R*	*PMAIP1*	The protein encoded by this gene is a membrane-bound receptor and member of the melanocortin receptor family. The encoded protein interacts with members of the melanocortin family: alpha-, beta- and gamma-melanocyte stimulating hormones	The *MC4R* transcript is expressed around the median level in most tissues. Most normal tissues displayed moderate cytoplasmic	Obesity (MIM #601665)	Body mass index (rs571312, Speliotes EK et al.), Body mass index (rs12970134, Thorleifsson G et al.), Weight (rs12970134,	

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					(MSH) and adrenocorticotropic (ACTH) hormones and is mediated by G proteins. The melanocortins are involved in a wide range of physiological functions, including pigmentation, energy homeostasis, inflammation, immunomodulation, steroidogenesis and temperature control.	protein staining. The intestine, renal tubuli, airway epithelium and trophoblastic cells exhibited strong membranous positivity. Exocrine pancreas and a subset of lymphoid cells showed strong cytoplasmic staining. Squamous epithelia, cells in the CNS and liver were mainly negative.		Thorleifsson G et al.), Waist circumference and related phenotypes (rs12970134, Chambers JC et al.), Obesity (rs17782313, Meyre D et al.), Body mass index (rs17782313, Willer CJ et al.), Body mass index (rs17782313, Loos RJ et al.), Waist circumference (rs489693, Heard-Costa NL et al.), Obesity (extreme) (rs10871777, Scherag A et al.)	
candidate	rs4149178	6 43367500 43544000	*SLC22A7*	*ZNF318 DLK2 CRIP3 ABCC10*	*SLC22A7* encodes for an organic anion transporter localized to liver and kidney cells[161]. In the kidney, it localizes to the basolateral membrane of proximal tubular cells where it mediates uptake of organic anions from the blood. Recently, it was shown that SLC22A7 transported urate in HEK293 cells stably expressing the transporter[162].	The SLC22A7 transcript and protein is very highly expressed in the liver, followed by the kidney (BioGPS and HPRD).	none		
network	rs884080	1 1867198 2023698	*PRKCZ*	*KIAA1751 GABRD*	*PRKCZ* is a member of the PKC family of serine/threonine kinase classified as atypical as not requiring calcium and diacylglycerol for activation. Alternative splicing is generating at least 2 different isoforms: PKCzeta and PKMzeta. The former is a key regulator of intracellular signaling pathways induced by various extracellular stimuli[163], e.g its activation, thought to be downstream of PI3K's, is required for insulin stimulation of glucose transport in myotubules and adipocyte cell culture[164,165]. The latter, PKMzeta, is brain specific and involves in long term potentiation[166]. In human kidney, PDZCzeta has been pulled by yeast two-hybrid as interacting directly with *SLC22A8*, and functional studies in rodent indicated that activation of PKCzeta by insulin or EFG increased *SLC22A6* and *SLC22A8* anion transport activity[167]. These transporters located at the basolateral membrane of proximal tubules mediated drug elimination but also urate secretion[168].	Protein detected in all tissues at variable levels, with strongest expression observed in CNS and pancreas.	none		
network	rs4970988	1 148792051 149266551	*ARNT*	*GOLPH3L CTSK FAM63A SETDB1*	Aryl hydrocarbon receptor nuclear translocator is required for the	Transcript is expressed at median levels in	translocation creating a		

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				CTSS MCL1 LASS2 ANXA9 PRUNE HORMAD1 ENSA ADAMTSL4	translocation to the nucleus of the xenobiotic bound Ah receptor where the complex activates transcription of enzymes involved in xenobiotic response. It also forms a complex with HIF-alpha, the heterodimeric hypoxia-inducible transcription factor, HIF1, which mediates the activation of several genes including erythropoietin[169], VEGF[170], nitric oxyde synthase[171], several glycolytic enzymes[172], as well as *ABCG2* in cell cultures[173]. Experiments in rats suggest that the cross-talk between oxygen availability and glucose is mediated by HIF1[174]. Mice lacking ARNT in fat are protected against diet-induced obesity, glucose intolerance and insulin resistance [175]	most tissues (BioGPS). Protein detected in nucleus of most cell types.	fusion between *ETV6* and *ARNT* in acute myeloid leukemia (MIM #601626)		
network	rs10489401	1 184520466 185076966	*PTGS2*	*C1orf27 PRG4 PDC PLA2G4A OCLM TPR*	*PTGS2* encodes for the inducible form of prostaglandin-endoperoxide synthase (cyclooxygenase) that catalyzes the first rate-limiting step of convertion of arachidonic acid to prostaglandins. It is concerned with injury, inflammation and proliferation. In an animal model, the calcium-sensing receptor signaling cascade triggering the ion transports of the medullary thick ascending limb involve *PTGS2* and *NFAT*[176].	The transcript is highly expressed in pancreatic islets, bronchial epithelium cells and smooth muscle (BioGPS). The protein is detected selectively in gall bladder, urinary bladder and genital tract at high levels (HPA).	none		
network	rs6707470	2 158005738 158121238	*ACVR1C*	*PSCDBP*	*ACVR1C* encodes for a type I activin receptor, also known as ALK7. The combination of ACVR2A and ACVR1C is preferred for activin AB and B signaling[177]. Together with its co-receptors, ALK7 transduces signals that play an important role in glucose-stimulated insulin secretion, development, and glucose homeostatic control of pancreatic endocrine cells[178].	*ACVR1C* transcript expressed ubiquitously at median levels (BioGPS), protein expressed at highest levels in testis, prostate, renal tubules and thyroid (HPA).	none		
network	rs4972801	2 176447239 176636239	*HOXD12*		*HOXD12* belongs to the homeobox family of genes. The homeobox genes encode a highly conserved family of transcription factors that play an important role in morphogenesis in all multicellular organisms. Mammals possess four similar homeobox gene clusters, *HOXA*, *HOXB*, *HOXC* and *HOXD*, located on different chromosomes, consisting of 9 to 11 genes arranged in tandem. This gene is one of several homeobox *HOXD* genes located in a cluster on chromosome 2. Deletions that remove the entire *HOXD* gene cluster or	Expression of the transcript occurs in most tissues around the median level.	none		cortisone / urea (p=3.9E-6)

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					the 5' end of this cluster have been associated with severe limb and genital abnormalities. The exact role of this gene has not been determined.				
network	rs12468226	2 202668239 204153739	*BMPR2*	*ICA1L NOP5/NOP58 SNORD11 WDR12 CYP20A1 ALS2CR13 NBEAL1 NOP5/NOP58 ABI2 RAPH1 SUMO1 ALS2CR8 SNORD70*	*BMPR2* encodes a type II receptor structurally very similar to ACVR2A and binds to the bone morphogenetic proteins BMP-7, BMP-2 and, less efficiently, BMP-4. Shared ligands/receptors suggest crosstalks between the activin and BMP pathways. BMPs are involved in endochondral bone formation and embryogenesis.	Expression of the transcript occurs in most tissues around the median level.	Primary pulmonary hypertension (MIM #178600), Pulmonary venoocclusive disease (MIM #265450)		
network	rs300915	4 144145345 144556345	*GAB1*	*USP38*	The protein encoded by *GAB1* is a member of the IRS1-like multi-substrate docking protein family. It is an important mediator of branching tubulogenesis and plays a central role in cellular growth response, transformation and apoptosis. Two transcript variants encoding different isoforms have been found for this gene.	Expression of the transcript occurs in most tissues around the median level.	none		
network	rs4073745	5 176442000 176777000	*SLC34A1*	*RGS14 F12 PRELID1 PFN3 LMAN2 PRELID1 RAB24 MXD3 FGFR4 NSD1*	*SLC34A1* encodes for a type II sodium-phosphate cotransporter that is expressed in the brush-border membrane of renal proximal tubular cells where it mediates phosphate reabsorption.	Transcript is expressed at high levels only in kidney.	Fanconi renotubular syndrome 2 (MIM #613388), Nephrolithiasis/osteoporosis, hypophosphatemic, 1 (MIM #612286).		
network	rs7944548	11 358500 630000	*HRAS*	*KIAA1542 DRD4 IRF7 LRRC56 RASSF7 RNH1 SIGIRR TMEM16J SCT PKP3 PTDSS2 MUPCDH B4GALNT4*	*HRAS* belongs to the Ras oncogene family, whose members are related to the transforming genes of mammalian sarcoma retroviruses. The products encoded by these genes function in signal transduction pathways. These proteins can bind GTP and GDP, and they have intrinsic GTPase activity. This protein undergoes a continuous cycle of de- and re-palmitoylation, which regulates its rapid exchange between the plasma membrane and the Golgi apparatus.	Expression of the transcript occurs in most tissues around the median level, with higher expression levels in CNS tissue, epithelial cells and colorectal adenocarcinoma.	Mutations in this gene cause Costello Syndrome (MIM #218040).		
network	rs11056399	12 15245500 15457500	*PTPRO*	*RERG*	*PTPRO* encodes the transmembrane protein protein tyrosine phosphatase, receptor type, O. The enzyme catalyzes the reaction of protein tyrosine phosphate + H2O =	Transcript expression is high in fetal brain and immune cells. Protein expression: strong	Nephrotic syndrome, type 6 (MIM #614196)		

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					protein tyrosine + phosphate.	cytoplasmic and membranous positivity was observed in renal glomeruli. Remaining normal tissues were negativ.			
network	rs4760636	12 46224500 46471000	*HDAC7*	*RAPGEF3 P11 RPAP3*	The protein encoded by *HDAC7* has sequence homology to members of the histone deacetylase family. HDAC7 is expressed in the early stages of embryonic development and suggested to play a role endothelial proliferation and growth[179]. Phosphorylation of HDAC7 mediates VEGF signaling towards endothelial cell proliferation and function[180]. VEGFa is also a novel urate loci candidate.	Expression of the transcript occurs in most tissues around the median level.	none		2-stearoylglycerophosphocholine * / caprate (10:0) (p=4.1E-6)
network	rs7976059	12 50262500 50802000	*ACVR1B/ACVRL1*	*ANKRD33 NR4A1 GRASP SCN8A C12orf44*	*ACVR1B* encodes the activin A receptor, type 1B. Activins are growth and differentiation factors of the TGF beta family. The receptor forms, upon activation, a complex with other type 1 and type 2 receptor subunits (among them *ACVR2A*) and activates the transcriptional regulator SMAD. The adjacent gene *ACVRL1* encodes the activin A receptor, type II-like 1 which also is a cell-surface receptor and part of the activin receptor complex. It also binds TGFbeta. It has a role in arterial development.	*ACVR1B*: transcript expressed ubiquitously, protein also expressed ubiquitously with highest levels in GI tract, liver and pancreas. *ACVRL1*: transcript expression highest in lung and heart. Protein expression: Seminiferus ducts, gall bladder, renal tubules, intestinal tract and neuronal cells in CNS showed strong cytoplasmic immunoreactivity.	*ACVRL1*: hereditary hemorrhagic telangiectasia type 2 (MIM #600376)		
network	rs7953704	12 120967163 121238073	*B3GNT4*	*MLXIP BCL7A IL31*	*B3GNT4* encodes a member of the beta-1,3-N-acetylglucosaminyltransferase protein family. The encoded enzyme is involved in the biosynthesis of poly-N-acetyllactosamine chains and prefers lacto-N-neotetraose as a substrate. It is a type II transmembrane protein.	Expression of the transcript occurs in most tissues around the median level.	none		
network	rs11624421	14 75593500 76126500	*ESRRB*	*BCYRN1 C14orf179 C14orf118*	*ESRRB* encodes a protein with similarity to the estrogen receptor. Its function is unknown; however, a similar protein in mouse plays an essential role in placental development.	Expression of the transcript occurs in most tissues around the median level.	Autosomal-recessive deafness (MIM #608565)		
network	rs3751043	15 61573000 61973000	*USP3*	*HERC1 FBXL22*	Ubiquitin specific peptidase 3 encodes a hydrolase that deubiquitinates monoubiquitinated target proteins such as histone H2A and H2B [GeneCards].	Expression of the transcript occurs primarily in lymphoid tissues.	none		
network	rs2472297	15 72496500	*CSK*	*MPI RPP25*	C-src tyrosine kinase; this protein	High cytoplasmic	none	Caffeine consumption	

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		73063000		*COX5A LMAN1L CPLX3 C15orf17 SCAMP2 UBL7 CLK3 CYP1A2 CYP1A1 SEMA7A ARID3B EDC3 ULK3*	specifically phosphorylates Tyr-504 residue on human leukocyte-specific protein tyrosine kinase, which acts as a negative regulatory site. It may also act on the LYN and FYN kinases.	expression in neurons in CNS. Also expressed in a few other cell types e.g in pancreas and placenta but at lower levels.		(rs2470893, Cornelis MC et al.), Coffee consumption (rs2472297, Sulem P et al.)	
network	rs11574736	20 42471000 42495500	*HNF4A*		The protein encoded by this gene, hepatocyte nuclear factor 4-alpha, is a nuclear transcription factor which binds DNA as a homodimer. The encoded protein controls the expression of several genes, including hepatocyte nuclear factor 1 alpha, a transcription factor which regulates the expression of several hepatic genes. This gene may play a role in development of the liver, kidney, and intestines. Mutations in this gene have been associated with monogenic autosomal dominant non-insulin-dependent diabetes mellitus type I. Alternative splicing of this gene results in multiple transcript variants.	Nuclear expression in intestinal tract, liver and kidney.	Maturity-onset diabetes of the young type 1; MODY1 (MIM #125850)		

1 Recombination interval as obtained from GRAIL.
2 Core gene: closest gene according to b36.
3 Genes in recombination interval as given by GRAIL. Manually-curated additonal core genes are in brackets and selected if predicted to be the gene underlying the association by GRAIL; genes that were removed from potential core gene because the causal gene in the region is known are in strike-through. The causal gene was assumed to be known when multiple association studies confirmed association of genic variants with serum urate, several lines of experimental evidence confirmed urate transport by the encoded protein, and no other urate transporters are known to be encoded by one of the additional genes in the recombination interval.
4 Expression at the transcript level obtained from bioGPS, expression on protein level obtained from Human Protein Atlas (HPA, only strong and moderate expression reported) or the Human Protein Reference Database (HPRD).
5 The field indicates trait, SNP (if not lead SNP), first author. If no rs ID is given, the GWAS hit matches the lead SNP reported. Only SNPs with $r^2>0.5$ are reported. Data available at www.genome.gov/gwastudies. Accessed July 17, 2011.

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Supplementary Table 8: X chromosomal SNPs Associated with Serum Urate at p<1*10^{-4}

discovery sample	SNP	bp (b36)	A1	A2	effect (mg/dl)	s.e.	p-value	n	I^2
overall	rs12859621	8924736	a	g	0.024	0.006	9.7E-05	63390	0
men	rs12556430	29523961	a	c	0.068	0.017	9.2E-05	23373	0
women	rs4826248	77258931	t	c	0.041	0.010	8.0E-05	37548	3
overall	rs4907821	102150170	t	c	0.024	0.006	5.0E-05	70723	27
overall	rs12833471	102171211	t	c	0.064	0.016	4.6E-05	59725	0
men	rs12833471	102171211	t	c	0.081	0.021	8.2E-05	27145	2
overall	rs5945761	102253461	t	c	-0.027	0.006	3.6E-05	56119	45
overall	rs5945942	102271854	c	g	-0.027	0.006	3.7E-05	56119	45
overall	rs11797302	102303221	a	g	-0.027	0.006	3.9E-05	56104	47
overall	rs5987509	102311938	t	c	-0.026	0.006	6.2E-05	56143	41
overall	rs5987697	102329964	t	c	-0.027	0.006	9.9E-06	61598	43
women	rs5987697	102329964	t	c	-0.037	0.009	4.0E-05	34228	0
overall	rs978853	102332334	t	c	-0.024	0.006	4.4E-05	62102	38
overall	rs727656	102360149	a	g	0.024	0.006	5.2E-05	62220	38
women	rs727656	102360149	a	g	0.036	0.009	7.7E-05	33715	0
overall	rs4907879	102360939	a	c	-0.026	0.006	2.8E-05	60483	41
women	rs4907879	102360939	a	c	-0.036	0.009	8.5E-05	33710	0
overall	rs743767	102372513	t	c	0.023	0.006	3.3E-05	70774	34
overall	rs6621632	102381248	a	g	-0.024	0.006	2.4E-05	71909	29
overall	rs2983090	102423718	a	t	-0.026	0.007	8.0E-05	55920	45
women	rs2983090	102423718	a	t	-0.041	0.010	3.6E-05	30722	0
women	rs2858106	102436869	t	c	0.042	0.010	3.2E-05	30669	0
overall	rs2743709	102446504	t	c	-0.024	0.006	2.2E-05	70774	38
women	rs2743709	102446504	t	c	-0.039	0.009	7.0E-06	38601	0
overall	rs2246252	102451859	c	g	-0.026	0.006	4.9E-05	56177	46
women	rs2246252	102451859	c	g	-0.045	0.010	2.3E-06	30910	0
overall	rs2743707	102457485	t	c	0.026	0.006	4.9E-05	56180	46
women	rs2743707	102457485	t	c	0.045	0.010	2.3E-06	30911	0
overall	rs2743706	102457896	a	g	0.026	0.006	4.9E-05	56180	46
women	rs2743706	102457896	a	g	0.045	0.010	2.3E-06	30911	0
overall	rs5945968	102461220	a	g	0.024	0.006	1.6E-05	70799	36
women	rs5945968	102461220	a	g	0.038	0.009	9.5E-06	38621	0
overall	rs5987515	102465559	t	g	-0.026	0.006	5.3E-05	56173	46
women	rs5987515	102465559	t	g	-0.045	0.010	2.8E-06	30908	0
overall	rs5987724	102465772	a	c	-0.026	0.006	4.4E-05	56181	46
women	rs5987724	102465772	a	c	-0.045	0.010	2.2E-06	30912	0
overall	rs5945971	102470061	t	c	-0.027	0.006	3.0E-05	56174	47
women	rs5945971	102470061	t	c	-0.045	0.010	2.4E-06	30907	0
overall	rs1045761	102472558	c	g	0.027	0.006	1.4E-05	56136	54
women	rs1045761	102472558	c	g	0.043	0.009	3.0E-06	30904	25
overall	rs5945767	102478099	t	c	-0.028	0.007	5.6E-05	51875	42
overall	rs5945770	102481592	t	c	0.025	0.005	5.4E-06	70838	43
women	rs5945770	102481592	t	c	0.033	0.008	7.2E-05	38633	37
overall	rs5945681	102482252	a	c	0.026	0.006	1.6E-05	57319	50
women	rs5945681	102482252	a	c	0.044	0.009	1.7E-06	31454	21

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overall	rs5945682	102482305	a	g	0.028	0.007	6.3E-05	51829	41
overall	rs5945771	102487941	a	t	0.028	0.007	6.7E-05	51874	42
overall	rs5945684	102514550	t	c	-0.028	0.007	5.4E-05	55757	37
women	rs5945684	102514550	t	c	-0.044	0.011	3.3E-05	30614	0
women	rs12834545	102780114	a	g	0.040	0.010	8.9E-05	30774	25
women	rs5987557	102791388	a	t	-0.039	0.010	1.0E-04	30911	29
women	rs12851072	102811779	a	t	-0.040	0.010	7.4E-05	30891	25
women	rs5987559	102819675	c	g	0.042	0.010	4.7E-05	30896	24
women	rs6621725	102824099	t	c	0.042	0.010	4.4E-05	30833	25
men	rs5910089	123394763	a	c	0.062	0.015	3.4E-05	25261	7
women	rs12854061	125785524	t	c	0.056	0.013	2.5E-05	30762	16
women	rs5931716	125790926	a	g	-0.048	0.012	6.6E-05	31829	8
women	rs5931717	125791688	t	c	0.048	0.012	9.9E-05	30913	13

Abbreviations: A1: allele 1 = effect allele; freq: frequency; s.e.: standard error; n: sample size; I^2: heterogeneity measure.

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Supplementary Table 9: Sex-specific Effects for Urate-Associated SNPs

						Men-specific effect				Women-specific effect				Effect Difference	
SNP	chr	bp (b36)	closest gene	A1	A2	effect (mg/dl)	s.e.	n	p-value	effect (mg/dl)	s.e.	n	p-value	z score	p-value
rs1471633	1	144435096	*PDZK1*	a	c	0.069	0.008	49621	3.5E-15	0.054	0.007	59099	1.6E-14	1.31	1.9E-01
rs11264341	1	153418117	*TRIM46*	t	c	-0.055	0.009	47709	1.1E-08	-0.044	0.007	57425	9.1E-09	-0.88	3.8E-01
rs1260326	2	27584444	*GCKR*	t	c	0.091	0.009	49808	3.0E-25	0.063	0.007	60491	1.1E-18	2.65	7.9E-03
rs17050272	2	121022910	*INHBB*	a	g	0.049	0.010	47359	6.5E-07	0.030	0.008	56259	1.9E-04	1.57	1.2E-01
rs2307394	2	148432898	*ORC4L*	t	c	-0.036	0.009	49788	1.2E-04	-0.034	0.007	59958	4.7E-06	-0.12	9.0E-01
rs6770152	3	53075254	*SFMBT1*	t	g	-0.052	0.009	49741	6.7E-09	-0.047	0.007	60252	6.0E-11	-0.45	6.5E-01
rs12498742	4	9553150	*SLC2A9*	a	g	0.269	0.010	49773	6.4E-153	0.460	0.008	60372	0*	-15.06	2.8E-51
rs11099098	4	81388936	*FGF5*	t	g	-0.039	0.010	46850	1.2E-04	-0.028	0.008	56605	7.3E-04	-0.91	3.7E-01
rs2231142	4	89271347	*ABCG2*	t	g	0.270	0.014	49764	3.8E-75	0.181	0.011	60433	1.3E-52	4.84	1.3E-06
rs17632159	5	72467238	*TMEM171*	c	g	-0.043	0.010	49306	1.3E-05	-0.039	0.008	58951	1.1E-06	-0.34	7.4E-01
rs675209	6	7047083	*RREB1*	t	c	0.060	0.010	49665	3.3E-09	0.064	0.008	60332	2.0E-15	-0.36	7.2E-01
rs1165151	6	25929595	*SLC17A1*	t	g	-0.096	0.008	49771	1.3E-28	-0.089	0.007	60278	4.2E-37	-0.66	5.1E-01
rs729761	6	43912549	*VEGFA*	t	g	-0.047	0.010	49619	3.2E-06	-0.047	0.008	59191	8.1E-09	-0.01	9.9E-01
rs1178977	7	72494985	*BAZ1B*	a	g	0.055	0.011	49543	8.2E-07	0.046	0.009	60030	2.6E-07	0.62	5.4E-01
rs10480300	7	151036938	*PRKAG2*	t	c	0.043	0.010	48984	1.7E-05	0.024	0.008	59371	3.2E-03	1.56	1.2E-01
rs17786744	8	23832951	*STC1*	a	g	-0.033	0.009	49743	2.1E-04	-0.029	0.007	60317	5.0E-05	-0.36	7.2E-01
rs2941484	8	76641323	*HNF4G*	t	c	0.048	0.009	49742	6.2E-08	0.046	0.007	60265	1.3E-10	0.20	8.4E-01
rs10813960	9	33170362	*B4GALT1*	t	c	-0.039	0.010	46321	1.7E-04	-0.031	0.008	55927	2.3E-04	-0.65	5.2E-01
rs10821905	10	52316099	*A1CF*	a	g	0.042	0.011	48832	3.8E-04	0.060	0.009	59081	2.5E-10	-1.22	2.2E-01
rs1171614	10	61139544	*SLC16A9*	t	c	-0.086	0.011	46927	1.9E-13	-0.067	0.009	56874	3.0E-13	-1.29	2.0E-01
rs1493664	11	25657565	*LUZP2*	t	c	-0.029	0.009	47767	1.1E-03	-0.029	0.007	57862	6.5E-05	-0.05	9.6E-01
rs2078267	11	64090690	*SLC22A11*	t	c	-0.085	0.009	44781	2.9E-19	-0.071	0.007	53228	5.7E-20	-1.19	2.4E-01
rs478607	11	64234639	*NRXN2*	a	g	-0.058	0.012	49533	9.6E-07	-0.043	0.009	60192	8.8E-06	-1.07	2.8E-01
rs642803	11	65317196	*OVOL1*	t	c	-0.047	0.008	49726	8.0E-08	-0.042	0.007	60273	2.1E-09	-0.45	6.6E-01
rs2195525	11	118740614	*USP2*	t	c	-0.034	0.009	49767	2.5E-04	-0.031	0.007	60442	3.5E-05	-0.30	7.7E-01
rs3741414	12	56130316	*INHBC*	t	c	-0.091	0.011	46327	7.0E-16	-0.057	0.009	56301	4.3E-10	-2.46	1.4E-02
rs653178	12	110492139	*ATXN2*	t	c	-0.044	0.009	49770	7.5E-07	-0.032	0.007	60453	5.5E-06	-1.07	2.9E-01
rs584480	13	71243506	*DACH1*	t	c	-0.034	0.009	49626	2.0E-04	-0.029	0.007	60199	6.3E-05	-0.41	6.8E-01

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rs4777542	15	70869419	*ADPGK*	t	c	-0.030	0.009	49289	1.6E-03	-0.034	0.007	56253	1.0E-05	0.39	7.0E-01
rs1394125	15	73946038	*UBE2Q2*	a	g	0.060	0.010	47741	6.3E-09	0.032	0.008	57826	1.0E-04	2.22	2.7E-02
rs6598541	15	97088658	*IGF1R*	a	g	0.039	0.009	49691	2.7E-05	0.050	0.007	59637	1.6E-11	-0.98	3.3E-01
rs7193778	16	68121391	*NFAT5*	t	c	-0.048	0.012	49733	2.1E-04	-0.045	0.010	60286	1.0E-05	-0.15	8.8E-01
rs7188445	16	78292488	*MAF*	a	g	-0.025	0.009	49748	7.9E-03	-0.040	0.007	60131	6.4E-08	1.37	1.7E-01
rs7224610	17	50719787	*HLF*	a	c	-0.043	0.009	49736	9.0E-07	-0.034	0.007	60412	3.0E-06	-0.90	3.7E-01
rs2079742	17	56820479	*BCAS3*	t	c	0.054	0.013	48562	5.6E-05	0.048	0.010	59065	1.0E-05	0.37	7.1E-01
rs164009	17	71795264	*QRICH2*	a	g	0.024	0.009	49716	6.2E-03	0.032	0.007	60057	8.2E-06	-0.70	4.8E-01
rs1035942	19	7150803	*INSR*	a	g	0.042	0.010	49700	2.0E-05	0.028	0.008	60222	4.6E-04	1.16	2.5E-01
rs4149178	6	43380166	*SLC22A7*	a	g	-0.058	0.012	49725	2.5E-06	-0.012	0.009	60289	2.1E-01	-3.00	2.7E-03
rs11757159	6	32628250	*HLA-DRB5*	t	c	-0.048	0.009	49757	3.6E-07	-0.011	0.007	59830	1.6E-01	-3.18	1.4E-03
rs11954519	5	39938122	*DAB2*	a	t	-0.005	0.010	46480	6.0E-01	-0.041	0.008	56627	4.6E-07	2.83	4.7E-03
rs456867	5	55846849	*ANKRD55*	t	c	-0.015	0.011	49806	2.0E-01	-0.046	0.009	60491	6.1E-07	2.19	2.8E-02
rs1933737	6	116416980	*FRK*	t	c	0.013	0.009	47607	1.8E-01	0.039	0.007	57561	5.8E-07	-2.15	3.1E-02
rs2244608	12	119901371	*HNF1A*	a	g	0.008	0.009	49692	3.9E-01	0.040	0.007	59938	1.6E-07	-2.72	6.6E-03
rs12955983	18	56023969	*MC4R*	a	g	-0.024	0.010	46457	2.3E-02	-0.042	0.008	56340	5.5E-07	1.42	1.6E-01

Effect estimates are provided from the discovery analyses. Gray font is used for non-replicating loci.*p-value was $<1*10^{-700}$

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Supplementary Table 10: All SNPs Associated with Gout at $p<1*10^{-6}$

Supplementary Table 10 is provided in a separate .xlsx document.

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Supplementary Table 11: Overall and Sex-Specific Associations with Prevalent and Incident Gout

					serum urate (mg/dl)			prevalent gout		incident gout		prevalent gout men		incident gout men		prevalent gout women		incident gout women	
SNP	discovery sample	closest gene	A1	A2	effect	s.e.	p-value	OR	p-value	OR	p-value	OR	p-value	OR	p-value	OR	p-value	OR	p-value
rs1471633	overall	*PDZK1*	a	c	0.061	0.005	1.4E-26	1.02	6.1E-01	1.09	1.7E-01	1.02	7.2E-01	1.05	5.0E-01	1.00	9.6E-01	1.16	1.6E-01
rs11264341	overall	*TRIM46*	t	c	-0.048	0.006	1.0E-14	0.92	1.9E-02	0.92	1.6E-01	0.95	2.5E-01	0.87	7.2E-02	0.90	5.1E-02	1.02	8.8E-01
rs1260326	overall	*GCKR*	t	c	0.077	0.006	1.3E-40	1.15	2.8E-05	1.12	6.9E-02	1.14	3.6E-03	1.15	7.1E-02	1.16	5.7E-03	1.07	5.6E-01
rs17050272	overall	*INHBB*	a	g	0.037	0.006	9.4E-09	1.03	5.1E-01	1.04	5.6E-01	1.04	5.0E-01	1.06	4.2E-01	1.04	4.7E-01	0.98	8.8E-01
rs2307394	overall	*ORC4L*	t	c	-0.035	0.006	7.3E-09	0.94	6.1E-02	0.97	6.0E-01	0.92	8.0E-02	1.00	9.9E-01	0.94	3.0E-01	0.91	3.8E-01
rs6770152	overall	*SFMBT1*	t	g	-0.048	0.006	2.7E-16	0.89	7.4E-04	0.91	1.3E-01	0.85	3.9E-04	0.93	3.1E-01	0.94	2.3E-01	0.88	2.3E-01
rs12498742	overall	*SLC2A9*	a	g	0.379	0.006	0*	1.57	5.2E-26	1.55	3.0E-08	1.65	3.1E-17	1.42	1.9E-04	1.49	6.8E-09	1.89	9.7E-06
rs11099098	overall	*FGF5*	t	g	-0.033	0.006	7.6E-07	0.92	3.6E-02	1.01	9.3E-01	0.96	4.4E-01	1.00	9.6E-01	0.90	8.1E-02	1.01	9.3E-01
rs2231142	overall	*ABCG2*	t	g	0.221	0.009	4.4E-116	1.71	6.9E-33	1.83	6.6E-10	1.96	1.6E-29	1.94	3.2E-08	1.41	4.3E-06	1.63	4.1E-03
rs17632159	overall	*TMEM171*	c	g	-0.038	0.006	2.0E-09	0.92	2.3E-02	0.89	9.7E-02	0.90	3.9E-02	0.88	1.2E-01	0.98	7.8E-01	0.93	5.1E-01
rs675209	overall	*RREB1*	t	c	0.063	0.006	1.4E-21	1.08	3.9E-02	1.14	9.0E-02	1.11	3.7E-02	1.09	3.5E-01	1.09	1.6E-01	1.25	1.0E-01
rs1165151	overall	*SLC17A1*	t	g	-0.093	0.005	4.5E-60	0.86	9.1E-06	0.85	1.0E-02	0.89	7.5E-03	0.84	2.0E-02	0.87	1.1E-02	0.88	2.6E-01
rs729761	overall	*VEGFA*	t	g	-0.046	0.006	3.1E-12	0.88	4.4E-04	0.85	2.2E-02	0.83	3.7E-04	0.78	4.8E-03	0.90	8.2E-02	1.00	9.9E-01
rs1178977	overall	*BAZ1B*	a	g	0.050	0.007	6.7E-12	1.13	4.5E-03	1.18	4.2E-02	1.10	1.1E-01	1.21	5.0E-02	1.14	5.7E-02	1.11	4.6E-01
rs10480300	overall	*PRKAG2*	t	c	0.032	0.006	9.4E-07	1.13	7.2E-04	0.97	7.0E-01	1.19	3.4E-04	1.03	7.5E-01	1.02	6.8E-01	0.87	2.4E-01
rs17786744	overall	*STC1*	a	g	-0.031	0.005	8.8E-08	0.95	8.7E-02	0.89	7.4E-02	0.93	1.2E-01	0.96	5.6E-01	0.93	1.8E-01	0.77	2.0E-02
rs2941484	overall	*HNF4G*	t	c	0.049	0.006	3.9E-17	1.02	5.0E-01	1.11	1.0E-01	1.04	3.7E-01	1.00	9.7E-01	1.02	6.8E-01	1.37	3.5E-03
rs10813960	overall	*B4GALT1*	t	c	-0.033	0.006	7.9E-07	0.91	1.8E-02	0.94	3.6E-01	0.92	1.1E-01	1.03	7.3E-01	0.90	1.1E-01	0.78	3.7E-02
rs10821905	overall	*A1CF*	a	g	0.053	0.007	3.4E-12	1.10	2.9E-02	1.06	4.5E-01	1.13	4.5E-02	1.04	6.9E-01	1.10	1.5E-01	1.10	4.6E-01
rs1171614	overall	*SLC16A9*	t	c	-0.074	0.007	6.5E-23	0.95	2.9E-01	0.79	3.0E-03	0.93	2.5E-01	0.73	1.6E-03	1.03	6.3E-01	0.91	4.9E-01
rs1493664	overall	*LUZP2*	t	c	-0.029	0.006	8.3E-07	0.98	5.6E-01	0.88	3.4E-02	0.98	6.7E-01	0.84	2.1E-02	1.00	9.3E-01	0.96	6.9E-01
rs2078267	overall	*SLC22A11*	t	c	-0.078	0.006	8.7E-36	0.86	4.4E-06	0.96	5.5E-01	0.85	2.8E-04	0.99	8.9E-01	0.89	2.8E-02	0.91	4.1E-01
rs478607	overall	*NRXN2*	a	g	-0.049	0.007	5.3E-10	0.97	4.7E-01	0.96	6.4E-01	0.98	8.0E-01	0.94	5.8E-01	0.94	3.7E-01	0.99	9.7E-01
rs642803	overall	*OVOL1*	t	c	-0.043	0.005	4.5E-14	0.91	6.8E-03	0.84	3.9E-03	0.89	8.8E-03	0.89	1.4E-01	0.93	2.0E-01	0.73	3.4E-03
rs2195525	overall	*USP2*	t	c	-0.031	0.006	2.6E-07	0.94	9.8E-02	1.17	1.1E-02	0.94	2.2E-01	1.20	1.4E-02	0.93	1.9E-01	1.10	3.6E-01
rs3741414	overall	*INHBC*	t	c	-0.071	0.007	9.8E-22	0.85	1.2E-04	0.95	5.0E-01	0.79	4.1E-05	0.90	3.0E-01	0.93	2.8E-01	1.04	7.9E-01
rs653178	overall	*ATXN2*	t	c	-0.036	0.005	2.4E-10	0.95	7.2E-02	0.97	6.0E-01	0.95	2.9E-01	0.93	3.8E-01	0.92	1.2E-01	1.04	7.4E-01
rs584480	overall	*DACH1*	t	c	-0.030	0.006	2.9E-07	0.94	8.6E-02	1.06	3.8E-01	0.93	1.3E-01	1.07	3.5E-01	0.94	2.8E-01	1.02	8.3E-01
rs4777542	overall	*ADPGK*	t	c	-0.033	0.006	1.5E-07	0.95	1.5E-01	1.04	5.1E-01	0.96	4.0E-01	0.97	7.1E-01	1.00	9.9E-01	1.21	9.7E-02

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rs1394125	overall	*UBE2Q2*	a	g	0.043	0.006	9.8E-11	1.03	4.2E-01	1.03	6.3E-01	1.09	7.2E-02	1.07	4.1E-01	0.94	2.9E-01	0.97	7.5E-01
rs6598541	overall	*IGF1R*	a	g	0.044	0.006	5.2E-13	1.06	7.9E-02	0.95	4.3E-01	1.09	6.4E-02	0.92	2.7E-01	0.98	6.7E-01	1.02	8.5E-01
rs7193778	overall	*NFAT5*	t	c	-0.047	0.008	2.4E-08	0.91	3.5E-02	0.94	5.2E-01	0.84	4.7E-03	0.97	8.0E-01	1.01	9.1E-01	0.89	4.5E-01
rs7188445	overall	*MAF*	a	g	-0.032	0.006	1.2E-07	0.98	4.8E-01	0.87	4.0E-02	0.96	3.9E-01	0.88	1.1E-01	1.01	8.6E-01	0.86	2.0E-01
rs7224610	overall	*HLF*	a	c	-0.038	0.006	4.7E-11	0.95	1.4E-01	0.98	7.5E-01	0.96	4.1E-01	1.12	1.6E-01	0.91	6.6E-02	0.77	1.3E-02
rs2079742	overall	*BCAS3*	t	c	0.051	0.008	6.2E-09	1.06	2.4E-01	0.98	8.7E-01	1.00	9.7E-01	0.96	7.4E-01	1.18	4.3E-02	1.04	8.3E-01
rs164009	overall	*QRICH2*	a	g	0.029	0.006	7.1E-07	1.09	6.7E-03	1.04	5.3E-01	1.08	9.1E-02	1.08	2.8E-01	1.12	4.2E-02	0.95	6.3E-01
rs1035942	overall	*INSR*	a	g	0.033	0.006	2.2E-07	1.01	7.4E-01	0.97	6.4E-01	1.02	6.3E-01	0.97	6.8E-01	0.99	8.1E-01	0.97	8.3E-01
rs4149178	candidate	*SLC22A7*	a	g	-0.032	0.008	1.9E-05	0.96	3.8E-01	0.92	3.2E-01	0.97	6.8E-01	0.89	2.8E-01	0.97	6.5E-01	0.97	8.4E-01
rs11757159	men	*HLA-DRB5*	t	c	-0.048	0.009	3.6E-07	0.94	2.0E-01	0.93	3.9E-01	0.94	2.0E-01	0.93	3.9E-01	1.00	9.8E-01	0.85	1.5E-01
rs11954519	women	*DAB2*	a	t	-0.041	0.008	4.6E-07	0.98	7.2E-01	0.89	3.2E-01	1.03	5.0E-01	0.99	8.9E-01	0.98	7.2E-01	0.89	3.2E-01
rs456867	women	*ANKRD55*	t	c	-0.046	0.009	6.1E-07	0.95	4.5E-01	1.07	6.3E-01	0.94	2.6E-01	1.03	8.0E-01	0.95	4.5E-01	1.07	6.3E-01
rs1933737	women	*FRK*	t	c	0.039	0.007	5.8E-07	1.01	9.1E-01	0.70	5.2E-03	1.03	5.6E-01	0.96	6.7E-01	1.01	9.1E-01	0.70	5.2E-03
rs2244608	women	*HNF1A*	a	g	0.040	0.007	1.6E-07	1.04	5.5E-01	1.16	2.0E-01	1.01	7.7E-01	0.88	1.1E-01	1.04	5.5E-01	1.16	2.0E-01
rs12955983	women	*MC4R*	a	g	-0.042	0.008	5.5E-07	1.02	7.3E-01	0.90	3.8E-01	0.94	1.8E-01	0.96	6.1E-01	1.02	7.3E-01	0.90	3.8E-01

Serum urate estimates are provided for the discovery sample. Gray font is used for non-replicating loci. Abbreviations: A1: allele 1 = effect allele; se: standard error; OR: odds ratio

The Pearson correlation between effects for prevalent and incident gout in the overall sample was 0.92 for replicated loci.

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Supplementary Table 12: Overall and Sex-Specific Association between SNPs and Fractional Excretion of Uric Acid (FEUA)

Supplementary Table 12 is provided in a separate .xlsx document.

Supplementary Table 13: Associations of Urate-Associated SNPs in African Americans and Individuals of Indian and Japanese Ancestry

Supplementary Table 13 is provided in a separate .xlsx document.

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Supplementary Table 14: Associations of Urate-Associated Index SNPs with Transcript Expression

eSNP	Tissue	p-value expression	expression probe	transcript	in *cis*	best eSNP for this transcript	r^2 between urate SNP and eSNP	urate SNP	chr	bp (b36)
rs1967017	Liver (UChicago)	1.9E-02	A_23_P161064	RNF115	1	rs1967017	1	rs1471633	1	144435096
rs4971100	SubCutAdipose (Greenawalt)	3.1E-07	10025903989	MUC1	1	rs4971100	1	rs11264341	1	153418117
rs4971100	SchadtLiver	2.2E-03		SLC39A1	1	rs4971100	1	rs11264341	1	153418117
rs1260326	Liver (Greenawalt)	1.5E-09	10025904647	C2orf16	1	rs1260326	Same SNP	rs1260326	2	27584444
rs1260326	Liver (UChicago)	1.2E-03	A_24_P222890	C2orf16	1	rs1260326	Same SNP	rs1260326	2	27584444
rs1260326	Liver (UWash)	2.0E-02	3780100	C2orf16	1	rs1260326	Same SNP	rs1260326	2	27584444
rs1260326	Liver (Greenawalt)	1.9E-05	10023816200	GCKR	1	rs1260326	Same SNP	rs1260326	2	27584444
rs780094	Liver (Greenawalt)	9.2E-13	10025914766	HSS00291930	0	rs780094	0.93	rs1260326	2	27584444
rs780094	Liver (Greenawalt)	4.1E-09	10025917899	XM_212496	0	rs780094	0.93	rs1260326	2	27584444
rs780093	Liver (UChicago)	4.7E-04	A_23_P406135	IFT172	1	rs780093	0.93	rs1260326	2	27584444
rs2911711	Liver (UChicago)	6.0E-03	A_23_P154058	EIF2B4	1	rs2911711	0.81	rs1260326	2	27584444
rs1260333	Liver (UChicago)	1.8E-02	A_23_P433132	KRTCAP3	1	rs1260333	0.81	rs1260326	2	27584444
rs17050272	Liver (UChicago)	3.3E-06	NA	INHBB	1	rs17050272	Same SNP	rs17050272	2	121022910
rs6706968	Liver (Greenawalt)	2.4E-14	10023810057	INHBB	1	rs6706968	0.97	rs17050272	2	121022910
rs6706968	SchadtLiver	2.7E-05		INHBB	1	rs6706968	0.97	rs17050272	2	121022910
rs2307394	omental	2.3E-05	10023817882	ACVR2A	1	rs2307394	Same SNP	rs2307394	2	148432898
rs2307394	Blood (Fehrmann et al)	3.7E-04	4590349	ACVR2A	1	rs12987286	Same SNP	rs2307394	2	148432898
rs12987286	Blood (Fehrmann et al)	3.2E-04	4590349	ACVR2A	1	rs12987286	1	rs2307394	2	148432898
rs12998729	SubCutAdipose (Greenawalt)	2.2E-07	10023817882	ACVR2A	1	rs12998729	1	rs2307394	2	148432898
rs2890915	Blood (Fehrmann et al)	3.7E-04	4590349	ACVR2A	1	rs12987286	1	rs2307394	2	148432898
rs2288190	SchadtLiver	7.1E-09		ACVR2A	1	rs2288190	0.84	rs2307394	2	148432898
rs6770152	PrefrontalCortex	8.4E-08	200667_at	UBE2D3	0	rs6770152	Same SNP	rs6770152	3	53075254
rs2581795	Liver (Greenawalt)	9.7E-05	10025902286	RFT1	1	rs2581795	0.84	rs6770152	3	53075254
rs2231142	Liver (Greenawalt)	2.2E-08	10033668963	ABCG2	1	rs2231142	Same SNP	rs2231142	4	89271347

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rs2231142	Liver (Greenawalt)	7.4E-08	10023825941	ABCG2	1	rs2231142	Same SNP	rs2231142	4	89271347
rs2231142	CR:Hunt	1.8E-09	10023813305	PKD2	1	rs2231142	Same SNP	rs2231142	4	89271347
rs9393672	VC:Alzh	2.8E-06	10023817545	HIST1H1C	1	rs9393672	1	rs1165151	6	25929595
rs942379	CD4+lymph	4.6E-06		SLC17A3	1	rs942379	0.97	rs1165151	6	25929595
rs11974409	omental	1.6E-08	10025910799	BAZ1B	1	rs11974409	1	rs1178977	7	72494985
rs11974409	SubCutAdipose (Greenawalt)	3.3E-05	10025910799	BAZ1B	1	rs11974409	1	rs1178977	7	72494985
rs11974409	Liver (UChicago)	4.5E-03	A_23_P123010	BCL7B	1	rs11974409	1	rs1178977	7	72494985
rs11974409	omental	1.4E-25	10023816986	MLXIPL	1	rs11974409	1	rs1178977	7	72494985
rs11974409	SubCutAdipose (Greenawalt)	2.6E-13	10025907760	MLXIPL	1	rs11974409	1	rs1178977	7	72494985
rs11974409	SubCutAdipose (Greenawalt)	2.3E-11	10023816986	MLXIPL	1	rs11974409	1	rs1178977	7	72494985
rs11974409	PFC:All	3.6E-08	10023816719	TBL2	1	rs11974409	1	rs1178977	7	72494985
rs11974409	SubCutAdipose (Greenawalt)	6.0E-06	10023816719	TBL2	1	rs11974409	1	rs1178977	7	72494985
rs11974409	VC:All	6.6E-06	10023816719	TBL2	1	rs11974409	1	rs1178977	7	72494985
rs6976930	omental	7.1E-22	10025907760	MLXIPL	1	rs11974409	1	rs1178977	7	72494985
rs10813960	Liver (UChicago)	2.7E-02	A_23_P146654	BAG1	1	rs10813960	Same SNP	rs10813960	9	33170362
rs10758192	Lymphocytes	1.6E-05		APTX	1	rs10758192	0.84	rs10813960	9	33170362
rs10813954	BcellsTransformed_HapMapJPT	1.0E-08	GI_13929461-S	B4GALT1	1	rs10813954	0.84	rs10813960	9	33170362
rs7036812	BcellsTransformed_HapMapYRI	7.2E-07	GI_13929461-S	B4GALT1	1	rs7036812	0.84	rs10813960	9	33170362
rs10758192	Blood (Fehrmann et al)	2.5E-06	3460386	B4GALT1	1	rs10758192	0.84	rs10813960	9	33170362
rs10758192	CD4+lymph	4.5E-08		B4GALT1	1	rs10758192	0.84	rs10813960	9	33170362
rs913214	LCL	8.0E-21	216627_s_at	B4GALT1	1	rs913214	0.84	rs10813960	9	33170362
rs10113903	BcellsTransformed_HapMapJPT	3.7E-08	GI_13929461-S	B4GALT1	1	rs10813954	0.84	rs10813960	9	33170362
rs10124479	BcellsTransformed_HapMapJPT	3.7E-08	GI_13929461-S	B4GALT1	1	rs10813954	0.84	rs10813960	9	33170362
rs10738905	BcellsTransformed_HapMapJPT	3.7E-08	GI_13929461-S	B4GALT1	1	rs10813954	0.84	rs10813960	9	33170362
rs10813950	BcellsTransformed_HapMapJPT	2.6E-08	GI_13929461-S	B4GALT1	1	rs10813954	0.84	rs10813960	9	33170362

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rs10971419	BcellsTransformed_HapMapJPT	2.7E-08	GI_13929461-S	B4GALT1	1	rs10813954	0.84	rs10813960	9	33170362
rs7036812	BcellsTransformed_HapMapJPT	1.1E-07	GI_13929461-S	B4GALT1	1	rs10813954	0.84	rs10813960	9	33170362
rs7849148	BcellsTransformed_HapMapJPT	2.8E-08	GI_13929461-S	B4GALT1	1	rs10813954	0.84	rs10813960	9	33170362
rs7865745	BcellsTransformed_HapMapJPT	3.7E-08	GI_13929461-S	B4GALT1	1	rs10813954	0.84	rs10813960	9	33170362
rs10758192	LCL	7.2E-18	216627_s_at	B4GALT1	1	rs913214	0.84	rs10813960	9	33170362
rs17300741	CR:Norm	7.6E-05	10031920868	DNAJC4	1	rs17300741	0.98	rs2078267	11	64090690
rs557675	Liver(UChicago)	4.1E-02	NA	DKFZp761E198	1	rs557675	1	rs642803	11	65317196
rs557675	CR:All	4.5E-05	10023807485	SLC29A2	1	rs557675	1	rs642803	11	65317196
rs653178	CR:All	9.6E-08	10023848139	CUX2	1	rs653178	Same SNP	rs653178	12	110492139
rs3184504	Liver(Greenawalt)	4.6E-26	10023848139	AL049919	1	rs3184504	1	rs653178	12	110492139
rs3184504	PFC:All	5.2E-41	10023848139	CUX2	1	rs3184504	1	rs653178	12	110492139
rs3184504	PFC:Alzh	3.2E-15	10023848139	CUX2	1	rs3184504	1	rs653178	12	110492139
rs3184504	PFC:Hunt	9.4E-17	10023848139	CUX2	1	rs3184504	1	rs653178	12	110492139
rs3184504	PFC:Norm	7.0E-11	10023848139	CUX2	1	rs3184504	1	rs653178	12	110492139
rs3184504	VC:All	6.1E-29	10023848139	CUX2	1	rs3184504	1	rs653178	12	110492139
rs3184504	VC:Alzh	9.7E-09	10023848139	CUX2	1	rs3184504	1	rs653178	12	110492139
rs3184504	VC:Hunt	1.8E-12	10023848139	CUX2	1	rs3184504	1	rs653178	12	110492139
rs3184504	Blood	2.0E-04	HSG00276844	FLJ21127	1	rs3184504	1	rs653178	12	110492139
rs2650000	Liver(Greenawalt)	2.3E-11	10023836323	LRRC19	0	rs2650000	0.92	rs2244608	12	119901371

The table only shows eSNPs for which the best eSNP for a given transcript is the same as or in perfect LD with the serum urate index SNP. Bold lines indicate alternating loci, whereas gray font indicates loci that did not replicate. The definition of *cis* varies somewhat across the datasets and is defined in the references describing the underlying expression datasets.

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Supplementary Table 15: Association of Replicated Urate-Associated SNPs with Related Phenotypes

Supplementary Table 15 is provided in a separate .xlsx document.

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Supplementary Table 16: Results from GRAIL Analyses of Urate-Associated SNPs from the Discovery Step

SNP	closest gene	GRAIL gene	GRAIL p-value
rs12498742	*SLC2A9*	*SLC2A9*	9.8E-09
rs1165151	*SLC17A1*	*SLC17A3*	3.1E-08
rs478607	*NRXN2*	*SLC22A12*	3.3E-08
rs1171614	*SLC16A9*	*SLC16A9*	6.6E-07
rs1260326	*GCKR*	*GCKR*	2.3E-06
rs2231142	*ABCG2*	*ABCG2*	8.6E-06
rs2078267	*SLC22A11*	*SLC22A11*	6.7E-05
rs1178977	*BAZ1B*	*MLXIPL*	1.1E-04
rs4777542	*ADPGK*	*ADPGK*	1.6E-04
rs1471633	*PDZK1*	*PDZK1*	9.1E-04
rs2307394	*ORC4L*	*ACVR2A*	1.1E-03
rs17050272	*INHBB*	*INHBB*	2.1E-03
rs1035942	*INSR*	*INSR*	3.2E-03
rs6598541	*IGF1R*	*IGF1R*	4.2E-03
rs3741414	*INHBC*	*INHBE*	8.7E-03
rs17786744	*STC1*	*STC1*	5.6E-02
rs11264341	*TRIM46*	*PKLR*	5.9E-02
rs2941484	*HNF4G*	*HNF4G*	6.9E-02
rs1394125	*UBE2Q2*	*NRG4*	1.5E-01
rs7188445	*MAF*	*MAF*	1.6E-01
rs11099098	*FGF5*	*FGF5*	1.9E-01
rs10480300	*PRKAG2*	*PRKAG2*	2.0E-01
rs653178	*ATXN2*	*PTPN11*	2.1E-01
rs584480	*DACH1*	*DACH1*	2.3E-01
rs2079742	*BCAS3*	*C17orf82*	2.3E-01
rs642803	*OVOL1*	*LTBP3*	3.0E-01
rs10813960	*B4GALT1*	*B4GALT1*	4.3E-01
rs2195525	*USP2*	*MFRP*	4.8E-01
rs729761	*VEGFA*	*VEGFA*	5.4E-01
rs17632159	*TMEM171*	*TMEM171*	6.0E-01
rs6770152	*SFMBT1*	*MUSTN1*	6.1E-01
rs7224610	*HLF*	*HLF*	6.6E-01
rs7193778	*NFAT5*	*NFAT5*	7.0E-01
rs10821905	*A1CF*	*ASAH2*	7.9E-01
rs675209	*RREB1*	*RREB1*	9.6E-01
rs164009	*QRICH2*	*PRPSAP1*	9.7E-01
rs1493664	*LUZP2*	N/A	N/A

Keywords describing the functional connections between the loci were 'activin', 'insulin', 'transporter', 'glucose', 'organic', 'anion', 'growth', 'renal', 'diabetes', 'serum', 'vegf', 'liver', 'pyruvate', 'factor', 'transporters', 'kidney', 'receptor', 'hepatocyte', 'type', and 'levels'.

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Supplementary Table 17: Functional Network Associations Underlying Supplementary Figure 8 and Supplementary Figure 9

Supplementary Table 17 is provided in a separate .xlsx document.

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Supplementary Table 18: Associated Pathways, Processes or Functions (p<1*10-3) Based on the Results from Ingenuity Pathway Analysis

Data base	set	alternative set/name	nominal p-value	genes associated with serum urate in the discovery screen
Networks	Gene Expression, Cell Cycle, Cellular Assembly and Organization		1.0E-28	ABCG2, ABCG5, ARID1A, B4GALT1, BAZ1A, BAZ1B, BAZ2A, BCAS3, CAPZB, DACH1, DEK, FGF5, MBD5, mir-153, mir-154, mir-664, MYBBP1A, MYC, NEUROD1, ORC4, PIM1, R3HDM2, RREB1, SCD, SF3B1, SLC16A9, SLC17A4, SLC2A9, SLK, SMARCC2, SMARCE1, SOCS2, TRIM38, UBE2U, ZNF274
Networks	Carbohydrate Metabolism, Small Molecule Biochemistry, Molecular Transport		1.0E-28	A1CF, ABCC2, ACACB, ADPGK, AP3D1, ATXN2, CLCN3, DLG4, EP300, GCKR, GTF3C1, GTF3C2, GTF3C3, GTF3C5, HNF4A, KHSRP, KLHL17, MAST2, mir-1, MLXIPL, MTX1, PDZK1, PEPCK, PKLR, PRPSAP1, PYGL, SAMM50, SLC17A, SLC17A1, SLC17A2, SLC22A11, TNPO2, TRAF6, TRIM46, USP2
Networks	Gene Expression, Cellular Movement, Cellular Compromise		1.0E-23	ADAM17, BATF3, BBS4, CEBPG, CELF2, DCN, EEA1, ERBB4, ERBB4 ligand, FOXA1, GALNT4, GIGYF1, HLF, HNF4G, KHSRP, LCP1, LMO2, MGRN1, mir-329, mir-379, mir-515, MUC1, NFAT5, NRG, NRG4, NRXN2, PDLIM5, QRICH2, RORB, SFMBT1, SNAI1, STC1, SUPT16H, UBE2Q2, ZNF512
Networks	Carbohydrate Metabolism, Molecular Transport, Endocrine System Disorders		1.0E-20	ACVR2A, ASAH2B, BAZ1A, BCL7B, DCN, EEA1, EHD1, EHD2, Focal adhesion kinase, GIPC1, GNAI1, IGF1R, INHBC, inhibin, INSR, Insulin, Irs3, IRS1/2, JAK1/2, mir-320, mir-491, mir-590, OVOL1, PDLIM5, PDPK1, PI3K (complex), PIK3C2B, PRKAG2, SH2B1, SH2B2, SH2B3, SLC17A3, SND1, TBL2, USP44
BioFunctions	Cellular Development/developmental process/developmental process of apud cells		1.6E-05	IGF1R, INSR, NRG4

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BioFunctions	Cellular Development/developmental process/developmental process of islet cells		2.3E-05	IGF1R, INSR, NRG4
BioFunctions	Organ Morphology/size/size of exocrine region of pancreas		5.2E-05	IGF1R, INSR
BioFunctions	Tissue Development/developmental process/developmental process of quadriceps femoris		5.2E-05	ACVR2A, STC1
BioFunctions	Tissue Development/developmental process/developmental process of gastrocnemius		8.7E-05	ACVR2A, STC1
BioFunctions	Carbohydrate Metabolism/transport/transport of carbohydrate	Molecular Transport/transport/transport of carbohydrate	1.0E-04	B4GALT1, INSR, PRKAG2, SLC17A3, SLC2A9
BioFunctions	Cellular Development/development/development of apud cells	Cellular Development/development/development of islet cells; Endocrine System Development and Function/development/development of apud cells; Endocrine System Development and Function/development/development of islet cells	1.3E-04	IGF1R, NRG4
BioFunctions	Carbohydrate Metabolism/glycolysis/glycolysis of cells		1.5E-04	INSR, MLXIPL, PRKAG2
BioFunctions	Carbohydrate Metabolism/import/import of carbohydrate	Molecular Transport/import/import of carbohydrate	2.8E-04	B4GALT1, INSR, PRKAG2
BioFunctions	Cell Death/self-renewal/self-		4.7E-04	IGF1R, MUC1

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	renewal of cell lines			
BioFunctions	Carbohydrate Metabolism/transport/transport of monosaccharide	Molecular Transport/transport/transport of monosaccharide	5.0E-04	INSR, PRKAG2, SLC17A3, SLC2A9
BioFunctions	Carbohydrate Metabolism/synthesis/synthesis of glycogen		6.8E-04	GCKR, IGF1R, INSR
BioFunctions	Cellular Development/developmental process/developmental process of beta islet cells		7.7E-04	IGF1R, INSR
BioFunctions	Embryonic Development/sex determination/sex determination of organism	Organismal Development/sex determination/sex determination of organism	8.9E-04	IGF1R, INSR

All genes written in gray font belong to the specified network (as selected by IPA algorithm) but were not included in the input gene set.

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Supplementary Note

Participating Studies

Studies included in the meta-analysis of serum urate GWAS: AGES Reykjavik Study, Amish, ARIC, ASPS, AUSTWIN, BLSA, BRIGHT, CARDIA, CHS, CoLaus, CROATIA-KORCULA, CROATIA-SPLIT, CROATIA-VIS, DESIR, EPIC-Norfolk cohort, ERF, Estonian Biobank, Family Heart Study, Framingham Heart Study, Health 2000, InCHIANTI, INCIPE, INGI-Carlantino, INGI-CILENTO, INGI-FVG, INGI-Val Borbera, KORA F3, KORA F4, LBC1936, Lifelines, LOLIPOP EW_A, LOLIPOP EW_P, LOLIPOP EW610, LURIC, MICROS, NESDA, NSPHS, ORCADES, PREVEND, PROCARDIS, RS-I, RS-II, SardiNIA, SHIP, SOCCS, Sorbs, TwinsUK, and Young Finns Study.

Studies included in the meta-analysis of gout GWAS: AGES Reykjavik Study, ARIC, ASPS, CHS, CoLaus, CROATIA-VIS, EPIC-Norfolk cohort, Framingham Heart Study, KORA F3, KORA F4, RS-I, RS-II, SHIP, and WGHS.

Replication studies with *in silico* GWAS data: EPIC cases, GHS I, GHS II, GSK, Hunter Community Study, Lifelines replication sample, LURIC GZ, LURIC HD, MARS, OGP Talana, SAPALDIA, SHIP-Trend.

Replication studies with *de novo* genotype data: HYPEST, KORA S2, and Ogliastra Genetic Park

Additional study samples: incident gout (HPFS and NHS), Indian ancestry (LOLIPOP), African Americans (ARIC, CARDIA, JHS from the CARe study[181]), Japanese ancestry (BioBank Japan).

Statistical Methods of Secondary Analyses

Analyses of the X Chromosome

X chromosome analyses were conducted in 19 studies with imputed data (AGES, ARIC, CHS, CoLaus, EPIC-Norfolk cohort, ERF, Estonian Biobank, FHS, INCIPE, INGI-CILENTO, INGI-Val Borbera, KORA F3, KORA F4, LBC1936, NESDA, RS-I, RS-II, SardiNIA, SHIP) and 6 studies with X chromosomal data available for genotyped SNPs only (Amish, AUSTWIN, BLSA, InCHIANTI, INGI-Carlantino, INGI-FVG). Imputation was performed using MACH[182] or IMPUTE[183] using the HapMap2 reference panel. Association tests were carried out similarly to the ones for autosomal SNPs, with men coded as homozygotes for their X chromosomal allele. Quality checks and meta-analysis were performed as for the autosomal analysis, but additional filters for MAF <5% and heterogeneity p-value $<5*10^{-8}$ were applied to the results. In total, 54,926 SNPs were analyzed in up to n=72,026 samples in the overall analysis, and separately for 52,897 SNPs in n=39,212 women and 55,210 SNPs in n=31,086 men.

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Analysis of Sex-Interactions

Genome-wide sex-interactions on the serum urate effect sizes were obtained by comparing, for each SNP, the discovery meta-analysis results from men (n= 49,825) and women (n= 60,522) using a *t*-test. Test statistics were calculated using the formula $t = (\beta_{men} - \beta_{women})/\mathrm{sqrt}(SE_{men}^2 + SE_{women}^2)$, assuming independent effect sizes between men and women. The correlation of the sex-stratified effect estimates using the whole dataset excluding the known urate-associated loci was r=0.08. Taking this correlation during computation of the combined SEs into account affected the estimation of sex-specific differences only marginally.

An alternative method consisting of a meta-analysis of the sex-differences within each cohort was also performed using the 45 populations for which both male and female-specific effects were available. The sex-difference was calculated as the difference between the female-specific effect and the male-specific effect in each population separately with the associated standard error for the difference estimate calculated as $\mathrm{sqrt}(SE_{men}^2 + SE_{women}^2)$, SE_{men} and SE_{women} being the genomic-control corrected standard errors of the SNP sex-specific estimates. An inverse-variance weighted meta-analysis of the sex-differences was performed using METAL[184]. The results were almost identical to those of the first analysis and are therefore not presented.

Gene-based Test

A gene-based test was conducted using the VEGAS software[185]. Briefly, this method assigns SNPs to genes and combines the association p-values accounting for LD between markers assigned to the same gene. Analyses were conducted using both urate and gout discovery meta-analysis datasets as input files. Genes with permutation p-values $<10^{-6}$ were manually reviewed for the presence of a common SNP in a gene that had not been identified in the primary meta-analysis. One such region was identified on chromosome 15, with SNP rs10851850 in *GRAMD2* having the lowest urate-associated p-value and a MAF of 0.28. The SNP was however not included in the final replication list because it was not independent of the nearby urate-associated variant rs4777542.

Evaluation of Evidence for Novel Urate Transporters

To evaluate the presence of potentially novel urate transport proteins that contain SNPs associated with serum urate at a sub-genome-wide significance level, we queried homologues of known urate transporters identified in GWAS for the presence of associated SNPs. We systematically interrogated SNPs in the ABC protein family (50 genes, known urate transporter encoded by *ABCG2*), the SLC2A family (14 genes, known urate transporter encoded by *SLC2A9*), the SLC17A family (9 genes, known urate transporters encoded by *SLC17A1* and *SLC17A3*), and the SLC22A family (23 genes, known urate transporters encoded by *SLC22A11*, *SLC22A12*). The number of independent SNPs in these 96 genes was estimated as 1759, using the HapMap2 and HapMap3 CEU r28 population as the reference. Analyses were conducted using the plink --indep option, including variants up to both 20 kb up- and downstream of each gene, 50 SNPs at a time, a window size of 5, and an r^2 of 0.5 to indicate independence. Based on a Bonferroni correction for 1759 variants, significant association was defined as p-value

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$<2.8*10^{-5}$. One gene region contained a variant meeting this threshold in association with urate, rs4149178 in *SLC22A7* ($p=1.9*10^{-5}$) and was therefore selected for replication.

Risk Score Analyses

A genetic risk score was generated to evaluate the combined effect of urate-increasing alleles on the risk of gout. The score was based on the 29 SNPs presented in **Supplementary Table 6** that showed an urate association p-value $<1*10^{-6}$ in the discovery stage and a decreased p-value after combining discovery and replication data. The number of urate-increasing alleles an individual carries at each of these loci was multiplied with the effect size of the respective allele from the discovery meta-analysis and summed across all loci. This estimate was then scaled by multiplying it by the number of SNPs divided by the sum of the effect sizes, to derive an individual's risk score that had a comparable range to a risk allele count. The risk score was then related to gout in three large population-based studies (ARIC, KORA F4, and SHIP; n=693 cases and n=11,714 controls) as well as in two independent nested case-control studies of incident gout over up to 22 years that were not part of the urate discovery analyses (NHS and HPFS; n=1,036 cases and n=1,091 controls). Logistic regression was used to estimate the odds ratio of gout per risk score unit increase. All models were adjusted for age and sex and study center if applicable. The proportion of individuals in each risk score category (rounded to the nearest integer) was calculated.

The following secondary analyses (f. to i.) were conducted for 44 SNPs identified for replication testing from the GWAS discovery meta-analyses (37 SNPs from urate overall), and from GWAS secondary analyses (1 for men, 5 for women, 1 for urate transporters), in order to better characterize the associations. The association with other traits is evaluated only for the 26 replicated loci from the overall analysis.

Association with the Fractional Excretion of Uric Acid (FEUA)

Urinary urate measures for the calculation of FEUA were available in the CROATIA-Split, CROATIA-Korcula, Hercules, PREVEND and Val Borbera studies. FEUA (%) was calculated, using the same units for the serum and urine measures, as ([urine urate]*[serum creatinine]*100)/([serum urate]*[urine creatinine]). Prior to analysis, FEUA was rank-transformed and age- and sex-adjusted residuals were obtained, with additional adjustment for study center and the first three principal components if necessary. These residuals were then related to each of urate-associated SNPs moved forward for replication using an additive genetic model and the dosages of the genotypes. Results from the individual studies were combined using an inverse-variance weighted meta-analysis. Results from a z-score based meta-analysis were comparable. As the purpose of this analysis was to help elucidate the physiological mechanism by which these urate-associated SNPs may influence serum urate levels, an alpha of 0.05 was used to indicate statistical significance.

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Association in Individuals of non-European Ancestries

To evaluate the generalizability of the urate-associated SNPs from the discovery stage, the SNPs were investigated in study samples of non-European ancestry as detailed in the **Methods**. Urate associations were estimated following the same statistical procedures and models as in the discovery cohorts.

Expression SNP (eSNP) Analyses

For each of the 44 sentinel QT SNPs all proxy SNPs with r2>0.8 were identified in HapMap CEU (releases 21, 22, and HapMap 3 vers. 2) using SNAP1 http://www.broadinstitute.org/mpg/snap/. Published associations between gene transcript levels and the genotype of nearby SNPs *in cis* for a wide spectrum of tissue/cell types were interrogated to assess the potential of the replicating candidate SNPs for eSNPs to influence gene expression. The tissues and cell types with available data were: fresh lymphocytes[186], fresh leukocytes[187], leukocyte samples in individuals with celiac disease[188], lymphoblastoid cell lines (LCL) derived from asthmatic children[189], HapMap LCL from 3 populations[190], a separate study on HapMap CEU LCL[191], peripheral blood monocytes[79,192], omental and subcutaneous adipose[193,194] and whole blood samples[193,195], 2 studies on brain cortex[175,192], 3 large studies of brain regions including prefrontal cortex, visual cortex and cerebellum (Emilsson, personal communication), liver[194,196,197], osteoblasts[198], skin[199] and additional fibroblast, T cell and LCL samples[200]. For each tissue or cell type, the citation describes the study-specific statistical criterion for establishing significant SNP associations. Only instances where a significant eSNP or a perfect proxy thereof was the eSNP with the lowest p-value for association with that transcript in the respective study are shown in **Supplementary Table 14**.

Associations of Urate-associated SNPs with Other Traits

We queried all 26 replicated urate-associated SNPs for their association with plasma C-reactive protein (CRP), systolic and diastolic blood pressure (SBP, DBP), stroke, myocardial infarction (MI), fasting glucose, fasting insulin, HOMA-B, HOMA-IR, 2-hour glucose and diabetes mellitus in GWAS results of other consortia. CRP was looked up in a dataset of n=66,185 participants of European ancestry[201]. The association between the urate SNPs and systolic and diastolic blood pressure was conducted among an effective sample size of n=46,356-69,815 individuals of European ancestry as published by the ICBP Consortium[202]. The association of the urate SNPs with stroke was looked up the datasets described in[203-206]. Associations with MI were looked up in GWAS data of CARDIoGRAM[207]. Data on glycaemic traits have been contributed by MAGIC investigators and have been downloaded from http://www.magicinvestigators.org, and data for association with type 2 diabetes were provided by the DIAGRAM Consortium[208].

To assess the combined effect of the urate-associated variants on these additional phenotypes, a genetic risk score was computed based on the 26 replicated SNPs using the method described previously[202], and related to the additional outcomes. Briefly, the regression on the risk score can be calculated using the regression effects and standard errors of each SNP on the corresponding phenotype, without further access to individual-level data. The coefficient and standard error of

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the risk score is a weighted mean of these per-SNP regression coefficients (matched to the urate-increasing allele) and the combined squared standard errors, respectively, where each is weighted by the effect size of the respective allele from the urate discovery meta-analysis. Using this method, the risk score was estimated and tested using the same statistical model and covariates as applied in the SNP specific analysis of the corresponding phenotype.

Pathway-based Analyses

To identify functional connections between the implicated genes and to test for the overrepresentation of certain gene sets, two approaches were used:

First, we incorporated pathway information via functional connections, most of them protein-protein interactions. For each of the 37 SNPs with p-values $<1*10^{-6}$ in the overall serum urate GWAS, we first identified the gene most likely to underlie the reported association using the Gene Relationships Among Implicated Loci (GRAIL) method[209]. Briefly, GRAIL determines one gene, which most likely underlies the observed association, along with an estimate of certainty. For rs1493664, GRAIL could not assign a gene and we therefore selected *LUZP2* as the closest gene in the genome to represent this locus. Further information about the most likely gene for each region as determined by GRAIL is provided in **Supplementary Table 16.** The resulting 37 GRAIL genes were used as seed genes to obtain direct functional associations from the STRING database[210] including the evidence types 'Experiments' and 'Databases' (without text mining), resulting in an urate-locus centered network containing 845 genes directly connected to a seed gene or the seed gene itself. For 6 seed genes (*TMEM171*, *MUSTN1*, *C17orf82*, *STC1*, *SLC16A9*, *LUZP2*) we did not obtain any functional associations from the STRING database according to our selection criteria. Networks based on two and three edge connections were also investigated. Each of the newly derived genes in a one edge neighborhood (ie, directly connected) was annotated with the SNP showing the smallest p-value in a 110KB upstream to 40KB downstream window[211] in the urate discovery meta-analysis. Of the 845 genes annotated in the network, 31 were seed genes, 33 were not annotated with any SNP according to the KB window, 40 SNPs were annotated to two of the genes and 3 appeared three times, resulting in a total of 735 unique new SNPs for further examination. Accordingly, we applied a new Bonferroni-corrected significance level $=0.05/735=6.80*10^{-5}$, a total of 27 different SNPs passed this cut-off. Of these, SNPs within 1 Mb or 2.5 Mb (*HLA* locus) of known regions were removed, leaving 19 SNPs, of which two pairs of SNPs were pruned due to high LD. As a result, 17 independent SNPs were subjected to validation testing among the *in silico* and *de novo* replication studies.

Second, we conducted an analysis using Ingenuity Pathway Analysis (IPA) software v9.0 (content version: 3210, release date: 2011-05-17), based on the 37 independent loci associated with serum urate at p-value $<1*10^{-6}$. IPA uses a comprehensive database containing various genes and gene products that interact with each other to select networks and functions enriched by the input genes. It tests a set of genes for enrichment in defined canonical pathways or functions and generates *de novo* networks of interacting genes or gene products. In the reference database, the Ingenuity Knowledge Base, all information regarding the interactions is maintained.

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Details on the IPA methods and algorithms can be found in the IPA Network Generation Algorithm whitepaper (October 29, 2005). In the 37 independent genomic regions containing SNPs associated with serum urate at p-value $<1*10^{-6}$, 55 genes were selected as input with at least one SNP in the transcribed region that had an $r^2>0.5$ with the lead SNP of the corresponding urate associated locus (*PKD2* has been manually removed of the *ABCG2* region due to its known non urate transport function). In IPA, endogenous chemicals were excluded from the search and only direct relationships with a high confidence (experimentally observed or highly predicted) were included. Data sources included in the analysis were Ingenuity Expert Informations (Ingenuity Expert Findings), Ingenuity Supported Third Party Informations (MircoRNA-mRNA interactions, miRecords, TarBase, TargetScan Human, Protein-protein interactions), BIND (BIOGRID, Cognia, DIP, INTACT, Interactome studies, MINT, MIPS), Additional Sources (ClinicalTrials.gov, Gene Ontology (GO), GVK Biosciences, Kyoto Encyclopedia of Genes and Genomes (KEGG), miRBase, Obesity Gene Map Database). Enriched (nominal p-value $<1*10^{-3}$) pathways and networks are listed in **Supplementary Table 17**.

The following secondary analyses (k. to m.) were conducted for 61 SNPs identified for replication testing from the GWAS discovery meta-analyses (37 SNPs from urate overall), GWAS secondary analyses (1 for men, 5 for women, 1 for urate transporters), and 17 SNPs identified in network analyses in order to better characterize the associations.

Association with Serum Metabolite Concentrations

The association between the index SNP at the 61 loci considered for replication and the serum concentrations of 276 metabolites and 37,179 metabolite ratios were queried in 1,768 individuals of the KORA F4 study as provided at the GWAS server (http://metabolomics.helmholtz-muenchen.de/gwa/). Metabolites were measured using Metabolon and quality control of the data was conducted as described previously[126]. For each of the SNPs, results with p-values $<5*10^{-6}$ are reported in **Supplementary Table 7**.

Association with Other GWAS Results in the NHGRI Database

By use of a GWAS server at http://metabolomics.helmholtz-muenchen.de/gwa/, all 61 SNPs as well as SNPs in LD ($r^2>0.5$) were evaluated for their association with other traits according to the NHGRI GWAS catalog[212] as shown in **Supplementary Table 7**.

Regional Association Plots

Regional Association Plots were generated using the stand-alone version of LocusZoom[1]. Information about LD was obtained from HapMap CEU r28. Regional Association Plots for 44 primary and secondary GWAS loci are shown in **Supplementary Figure 2**. P-values at sex-specific loci (*HLA-DRB5*, *DAB2*, *ANKRD55*, *FRK*, *HNF1A*, *MC4R*) correspond to the sex-specific GWAS results. Regional Association Plots for the replicated network loci as shown in **Table 3** are shown in **Supplementary Figure 7**.

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De Novo Genotyping Information

Genotyping for KORA S2 and Ogliastra Genetic Park samples was performed at Helmholtz Zentrum München and genotyping of the HYPEST samples was performed at the University of Tartu with the MassARRAY system using the iPLEX technology (Sequenom, San Diego, CA). The allele-dependent primer extension products were loaded onto one 384-element chip using a nanoliter pipetting system (SpectroCHIP, Spectro-POINT Spotter, Sequenom at Helmholtz Zentrum München and MassARRAY Nanodispenser RS1000, Sequenom at the University of Tartu). The samples were analyzed by matrix-assisted laser desorptionionization time-of-flight mass spectrometry (Bruker Daltonik, Leipzig, Germany at the Helmholtz Zentrum München and MassARRAY Analyzer 4, Sequenom at the University of Tartu). The resulting mass spectra were analyzed for peak identification via the SpectroTYPER RT 3.4 software from Sequenom (Helmholtz Zentrum München) and the TyperAnalyzer 4.0 software (University of Tartu).

The designed plex for Ogliastra Genetic Park samples contained 30 SNPs: rs1035942 (*INSR*), rs10813960 (*B4GALT1*), rs11954519 (*DAB2*), rs12955983 (*MC4R*), rs1394125 (*UBE2Q2*), rs1493664 (*LUZP2*), rs17050272 (*INHBB*), rs1933737 (*FRK*), rs2079742 (*BCAS3*), rs2185631 (*ABCC10*), rs2195525 (*USP2*), rs2244608 (*HNF1A*), rs3184504 (*ATXN2*, proxy for rs653178, r^2=0.873), rs642803 (*OVOL1*), rs10821905 (*A1CF*), rs11757159 (*HLA-DRB5*), rs1178977 (*BAZ1B*), rs1458038 (*FGF5*, proxy for rs11099098, r^2=1), rs157510 (*ANKRD55*, proxy for rs456867, r^2=1), rs164009 (*QRICH2*), rs17632159 (*TMEM171*), rs17786744 (*STC1*), rs4149178 (*SLC22A7*), rs4777542 (*ADPGK*), rs584480 (*DACH1*), rs6729465 (*ORC4L*, proxy for rs2307394, r^2=1), rs7188445 (*MAF*), rs7193778 (*NFAT5*), rs7224610 (*HLF*), and rs729761 (*VEGFA*). 27 of the selected 30 SNPs could be genotyped successfully. rs2185631 (*ABCC10*) could not be called properly whereas rs4777542 (*ADPGK*) and rs11757159 (*HLA-DRB5*) had to be removed due to HWE discrepancies. 9,556 individuals were genotyped with call rates above 0.9 and used for the replication analysis.

The designed plex for HYPEST and KORA S2 contained the following 30 SNPs: rs2941484 (*HNF4G*), rs642803 (*OVOL1*), rs6729465 (*ORC4L*, proxy for rs2307394, r^2=1), rs10480300 (*PRKAG2*), rs1035942 (*INSR*), rs10813960 (*B4GALT1*), rs11099098 (*FGF5*), rs7164727 (*ADPGK*, proxy for rs4777542, r^2=1), rs1493664 (*LUZP2*), rs500830 (*DACH1*, proxy for rs584480, r^2=0.966), rs2195525 (*USP2*), rs7953704 (*B3GNT4*), rs4970988 (*ARNT*), rs7976059 (*ACVR1B/ACVRL1*), rs4073745 (*SLC34A1*), rs11574736 (*HNF4A*), rs4760636 (*HDAC7*), rs2472297 (*CSK*), rs16824599 (*BMPR2*, proxy for rs12468226, r^2=1), rs4972801 (*HOXD12*), rs12614722 (*ACVR1C*, proxy for rs6707470, r^2=1), rs300913 (*GAB1*, proxy for rs300915, r^2=1), rs11056399 (*PTPRO*), rs884080 (*PRKCZ*), rs4984252 (*USP3*, proxy for rs3751043, r^2=1), rs4963135 (*HR4S*, proxy for rs7944548, r^2=1), rs10489401 (*PTGS2*), rs7141815 (*ESRRB*, proxy for rs11624421, r^2=1), rs7732943 (*DAB2*, proxy for rs11954519, r^2=0.963), and rs2244608 (*HNF1A*). In KORA S2, 25 of the selected 30 SNPs could be genotyped successfully. rs11056399 (*PTPRO*) and rs11099098 (*FGF5*) could not be called whereas rs500830 (*DACH1*), rs6729465 (*ORC4L*), and rs4972801 (*HOXD12*) were removed due to call rates below 0.9. 3,685 individuals were genotyped with call rates above 0.9 and used for the replication analysis. In

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HYPEST 24 of the selected 30 SNPs could be genotyped successfully. rs11099098 (*FGF5*) could not be called and rs11056399 (*PTPRO*), rs2472297 (*CSK*), rs4963135 (*HR4S*), rs4972801 (*HOXD12*), and rs500830 (*D4CH1*) were removed due to call rates below 0.9. The HYPEST study included 751 samples.

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Supplementary Text 1: Replicated Urate GWAS Loci in the Inhibins-Activins Pathway

Inhibins and activins are part of the transforming growth factor-beta (TGF-) superfamily of growth and differentiation factors. They are dimers composed of alpha and/or beta subunits and signal through transmembrane receptors that are heteromeric complexes of type I and II serine threonine kinase subunits.

INHBB encodes for the inhibin beta subunit B that together with inhibin beta subunit A forms activin B, which has effects on gonadal function, reproduction and fetal development. A singularity of INHBB is its high mRNA expression in adipose tissues. Activin B has been proposed as a novel adipokine, a role likely dependent on signaling through the receptor I ACVR1C[213], a suggestive urate-locus in our analysis (**Supplementary Table 7**). Data in mice knocked-out for *ACVR1C*, *INHBB* and double mutants suggest that activin B and ACVR1C both influence insulin secretion[214], and INHBB transcript levels in human adipose tissues correlate with serum fasting insulin concentrations[215]. INHBB and AVCR1C proteins have been detected in the renal tubules as well. Their downstream signaling targets are currently unknown.

INHBC/ INHBE:

INHBC encodes for the inhibin beta subunit C, which was cloned from human liver[216]. Its function is still poorly characterized; it dimerizes with the beta A and B (encoded by *INHBB*) subunits *in vitro*.

INHBE encodes the fourth characterized human inhibin beta subunit, E, also cloned from human liver tissue[217]. Experiments in rats suggest that INHBE transcript levels in liver respond to feeding status[218]. The INHBE promoter contains binding elements for the C/EBP transcription factors involved in regulation of metabolic homeostasis[219]. In contrast to the broad expression pattern of INHBA and INHBB, INHBE is predominantly expressed in liver.

ACVR1B/ ACVRL1:

ACVR1B encodes for a type I receptor (ALK4) able to form a complex with ACVR2A, a suggestive urate-locus in our analysis (**Supplementray Table 7**). It transduces signals of a broader spectrum of ligands than the suggestive urate-locus ACVR1C but phosphorylates the same downstream effectors, Smad 2 and 3, part of the "TGFb/activin" pathway. ***RREB1***, a transcription factor also identified as a replicated urate-locus, has been reported to bind to the RAS-responsive elements of the *ACVR1B* gene promoter.

ACVRL1 also encodes for a type I receptor, ALK1, able to form a complex with ACVR2A. It induces the phosphorylation of a different set of downstream effectors than ACVR1B and part of the "BMP pathway" kinases. Mutations in this gene have been reported as a cause of hemorrhagic telangiectasia type 2 (MIM:600376).

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Supplementary Text 2: Replicated Genes Regulating Glucose Metabolism

Genetic variants acting directly or indirectly on glycolysis could modulate urate levels in at least two ways: by altering the amount of lactate or other organic anions, which can affect urate transport, and by tuning *de novo* purine synthesis via the pentose phosphate pathway (PPP). Both processes have been well documented to account for the hyperuricemia co-occuring with gross alteration of glycolytic flux in type I glycogen storage disease (MIM #232200)[220].

GCKR: in hepatocytes, the product of GCKR inhibits glucokinase that catalyzes the first reaction of glycogen synthesis and glycolysis[221]. Common *GCKR* variants have been associated with a variety of medically-relevant traits. Fructose, a recognized dietary enhancer of urate levels, and phosphorylation by AMP-activated kinase (AMPK), a subunit of which is among the newly identified urate genes (***PRKAG2***), modulate GCKR-mediated glucokinase inhibition[222].

PKLR encodes the liver and erythrocyte enzyme that catalyzes the last, rate-limiting, step of glycolysis, generating ATP and pyruvate. Pyruvate is - under normoxia - mostly converted to acetyl-coenzymeA, but can also be converted to lactate which is known to lower urinary urate secretion[223]. In rats, **MLXIPL**, also identified here, is part of a complex recruited to the promoter of the *PKLR* homolog that mediates its glucose-induced expression and cAMP-induced repression[224].

MLXIPL encodes a glucose-responsive transcription factor, ChREBP, which upon binding to carbohydrate response elements regulates the transcription of genes involved in glycolysis (e.g. ***PKLR***) and lipogenesis in hepatocytes, pancreatic beta-cells and adipocytes. It acts as a repressor of the *ARNT* gene, a suggestive urate-associated locus (**Supplementary Table 7**), in pancreatic beta cells[225], and activates the transcription of ***INHBE***, a novel urate locus (**Supplementary Text 1**), under high glucose conditions[226].

PRKAG2 encodes the regulatory subunit gamma2 of the AMP-activated protein kinase (AMPK) complex, the key sensor of cellular AMP:ATP ratio that promotes glucose uptake and ATP-generating catabolic processes (e.g. glycolysis and pyruvate oxidation). AMPK is activated by the antidiabetic-drug metformin. The transcription factors encoded by *HNF4A* and ***MLXIPL*** as well as **GCKR**, are potential direct targets of AMPK[222,227]. Over-expression of the gamma 2 subunit in mice and inappropriate activation of AMPK under the non-energy deficient state by mutations in *PRKAG2* in humans lead to increase glycogen storage in the heart[228]. AMPK has also been implicated in the regulation of renal uric acid excretion in birds[229].

NFAT5 encodes a transcription factor activated by osmotic stress. Under hyperglycemic conditions it upregulates aldose reductase, which activates the polyol pathway modifying glucose flux and increasing PPP activity[230]. The association with FEUA could be connected to altered ion transport regulation by the accumulation of organic osmolytes.

HNF4G: like its better functionally characterized structural homolog HNF4A, it encodes a member of the nuclear receptor superfamily of transcription factors of the nutrient uptake sensors subclass, predominantly expressed in gastro-/enterohepatic tissues[231]. A study of inter-transcription factor regulatory network in human hepatoma cells[232] places HNF4G as a receiver of multiple transcription factors regulatory signals (including HNF4A).

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Fasting insulin, fasting glucose, HOMA-B, HOMA-IR

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References

1. Pruim, R.J. et al. LocusZoom: regional visualization of genome-wide association scan results. Bioinformatics 26, 2336-7 (2010).
2. Harris, T.B. et al. Age, Gene/Environment Susceptibility-Reykjavik Study: multidisciplinary applied phenomics. American journal of epidemiology 165, 1076-87 (2007).
3. Mitchell, B.D. et al. The genetic response to short-term interventions affecting cardiovascular function: rationale and design of the Heredity and Phenotype Intervention (HAPI) Heart Study. American heart journal 155, 823-8 (2008).
4. McArdle, P.F. et al. Association of a common nonsynonymous variant in GLUT9 with serum uric acid levels in old order amish. Arthritis and rheumatism 58, 2874-81 (2008).
5. The Atherosclerosis Risk in Communities (ARIC) Study: design and objectives. The ARIC investigators. American journal of epidemiology 129, 687-702 (1989).
6. Iribarren, C., Folsom, A.R., Eckfeldt, J.H., McGovern, P.G. & Nieto, F.J. Correlates of uric acid and its association with asymptomatic carotid atherosclerosis: the ARIC Study. Atherosclerosis Risk in Communities. Annals of epidemiology 6, 331-40 (1996).
7. Eckfeldt, J.H., Chambless, L.E. & Shen, Y.L. Short-term, within-person variability in clinical chemistry test results. Experience from the Atherosclerosis Risk in Communities Study. Archives of pathology & laboratory medicine 118, 496-500 (1994).
8. Schmidt, R. et al. Assessment of cerebrovascular risk profiles in healthy persons: definition of research goals and the Austrian Stroke Prevention Study (ASPS). Neuroepidemiology 13, 308-13 (1994).
9. Whitfield, J.B., Zhu, G., Nestler, J.E., Heath, A.C. & Martin, N.G. Genetic covariation between serum gamma-glutamyltransferase activity and cardiovascular risk factors. Clinical chemistry 48, 1426-31 (2002).
10. Middelberg, R.P., Medland, S.E., Martin, N.G. & Whitfield, J.B. A longitudinal genetic study of uric acid and liver enzymes in adolescent twins. Twin research and human genetics : the official journal of the International Society for Twin Studies 10, 757-64 (2007).
11. Benyamin, B. et al. Common variants in TMPRSS6 are associated with iron status and erythrocyte volume. Nature genetics 41, 1173-5 (2009).
12. Shock, N.W. et al. Normal Human Aging: The Baltimore Study of Aging. U. S. Department of Health and Human Services (1984).
13. Caulfield, M. et al. Genome-wide mapping of human loci for essential hypertension. Lancet 361, 2118-23 (2003).
14. Friedman, G.D. et al. CARDIA: study design, recruitment, and some characteristics of the examined subjects. Journal of clinical epidemiology 41, 1105-16 (1988).
15. Fried, L.P. et al. The Cardiovascular Health Study: design and rationale. Annals of epidemiology 1, 263-76 (1991).
16. Firmann, M. et al. The CoLaus study: a population-based study to investigate the epidemiology and genetic determinants of cardiovascular risk factors and metabolic syndrome. BMC cardiovascular disorders 8, 6 (2008).
17. Zemunik, T. et al. Genome-wide association study of biochemical traits in Korcula Island, Croatia. Croat Med J 50, 23-33 (2009).
18. Rudan, I. et al. "10001 Dalmatians:" Croatia launches its national biobank. Croat Med J 50, 4-6 (2009).
19. Vitart, V. et al. 3000 years of solitude: extreme differentiation in the island isolates of Dalmatia, Croatia. Eur J Hum Genet 14, 478-87 (2006).

Nature Genetics doi:10/1038/ng.2500

20. Balkau, B., Eschwege, E., Tichet, J. & Marre, M. Proposed criteria for the diagnosis of diabetes: evidence from a French epidemiological study (D.E.S.I.R.). Diabetes & metabolism 23, 428-34 (1997).
21. Vernay, M. et al. Alcohol consumption and insulin resistance syndrome parameters: associations and evolutions in a longitudinal analysis of the French DESIR cohort. Annals of epidemiology 14, 209-14 (2004).
22. Day, N. et al. EPIC-Norfolk: study design and characteristics of the cohort. European Prospective Investigation of Cancer. British journal of cancer 80 Suppl 1, 95-103 (1999).
23. Pardo, L.M., MacKay, I., Oostra, B., van Duijn, C.M. & Aulchenko, Y.S. The effect of genetic drift in a young genetically isolated population. Annals of human genetics 69, 288-95 (2005).
24. Nelis, M. et al. Genetic structure of Europeans: a view from the North-East. PloS one 4, e5472 (2009).
25. Metspalu, A., Kohler, F., Laschinski, G., Ganten, D. & Roots, I. [The Estonian Genome Project in the context of European genome research]. Deutsche medizinische Wochenschrift 129 Suppl 1, S25-8 (2004).
26. Higgins, M. et al. NHLBI Family Heart Study: objectives and design. American journal of epidemiology 143, 1219-28 (1996).
27. Neogi, T., Terkeltaub, R., Ellison, R.C., Hunt, S. & Zhang, Y. Serum Urate Is Not Associated with Coronary Artery Calcification: The NHLBI Family Heart Study. The Journal of rheumatology 38, 111-7 (2011).
28. Neogi, T. et al. Serum uric acid is associated with carotid plaques: the National Heart, Lung, and Blood Institute Family Heart Study. The Journal of rheumatology 36, 378-84 (2009).
29. Tang, W. et al. Familial clustering for features of the metabolic syndrome: the National Heart, Lung, and Blood Institute (NHLBI) Family Heart Study. Diabetes care 29, 631-6 (2006).
30. Tang, W. et al. Linkage analysis of a composite factor for the multiple metabolic syndrome: the National Heart, Lung, and Blood Institute Family Heart Study. Diabetes 52, 2840-7 (2003).
31. Wilk, J.B. et al. Segregation analysis of serum uric acid in the NHLBI Family Heart Study. Human genetics 106, 355-9 (2000).
32. Dawber, T.R., Kannel, W.B. & Lyell, L.P. An approach to longitudinal studies in a community: the Framingham Study. Annals of the New York Academy of Sciences 107, 539-56 (1963).
33. Crowley, L.V. Determination of Uric Acid: An Automated Analysis Based on a Carbonate Method. Clinical chemistry 10, 838-44 (1964).
34. Ferrucci, L. et al. Subsystems contributing to the decline in ability to walk: bridging the gap between epidemiology and geriatric practice in the InCHIANTI study. Journal of the American Geriatrics Society 48, 1618-25 (2000).
35. Gambaro, G. et al. Prevalence of CKD in northeastern Italy: results of the INCIPE study and comparison with NHANES. Clinical journal of the American Society of Nephrology : CJASN 5, 1946-53 (2010).
36. Tepper, B.J. et al. Variation in the bitter-taste receptor gene TAS2R38, and adiposity in a genetically isolated population in Southern Italy. Obesity 16, 2289-95 (2008).
37. Ciullo, M. et al. New susceptibility locus for hypertension on chromosome 8q by efficient pedigree-breaking in an Italian isolate. Human molecular genetics 15, 1735-43 (2006).
38. Colonna, V. et al. Campora: a young genetic isolate in South Italy. Human heredity 64, 123-35 (2007).
39. Ciullo, M. et al. Identification and replication of a novel obesity locus on chromosome 1q24 in isolated populations of Cilento. Diabetes 57, 783-90 (2008).
40. Sala, C. et al. Variation of hemoglobin levels in normal Italian populations from genetic isolates. Haematologica 93, 1372-5 (2008).

Nature Genetics doi:10/1038/ng.2500

41. Traglia, M. et al. Heritability and demographic analyses in the large isolated population of Val Borbera suggest advantages in mapping complex traits genes. PloSone 4, e7554 (2009).
42. Heid, I.M. et al. Meta-analysis of the INSIG2 association with obesity including 74,345 individuals: does heterogeneity of estimates relate to study design? PLoSgenetics 5, e1000694 (2009).
43. Colonna, V. et al. Comparing population structure as inferred from genealogical versus genetic information. European journal of human genetics : EJHG 17, 1635-41 (2009).
44. Bedin, E. et al. Age-related hearing loss in four Italian genetic isolates: an epidemiological study. International journal of audiology 48, 465-72 (2009).
45. Slervo, M. et al. Angiogenesis and biomarkers of cardiovascular risk in adults with metabolic syndrome. Journal of internal medicine 268, 338-47 (2010).
46. Girotto, G. et al. Hearing function and thresholds: a genome-wide association study in European isolated populations identifies new loci and pathways. Journal of medical genetics 48, 369-74 (2011).
47. Wichmann, H.E., Gieger, C. & Illig, T. KORA-gen--resource for population genetics, controls and a broad spectrum of disease phenotypes. Gesundheitswesen 67 Suppl 1, S26-30 (2005).
48. Deary, I.J. et al. The Lothian Birth Cohort 1936: a study to examine influences on cognitive ageing from age 11 to age 70 and beyond. BMC geriatrics 7, 28 (2007).
49. Houlihan, L.M. et al. Common variants of large effect in F12, KNG1, and HRG are associated with activated partial thromboplastin time. American journal of human genetics 86, 626-31 (2010).
50. Stolk, R.P. et al. Universal risk factors for multifactorial diseases: LifeLines: a three-generation population-based study. European journal of epidemiology 23, 67-74 (2008).
51. Yuan, X. et al. Population-based genome-wide association studies reveal six loci influencing plasma levels of liver enzymes. American journal of human genetics 83, 520-8 (2008).
52. Kooner, J.S. et al. Genome-wide scan identifies variation in MLXIPL associated with plasma triglycerides. Nature genetics 40, 149-51 (2008).
53. Winkelmann, B.R. et al. Rationale and design of the LURIC study--a resource for functional genomics, pharmacogenomics and long-term prognosis of cardiovascular disease. Pharmacogenomics 2, S1-73 (2001).
54. Pattaro, C. et al. The genetic study of three population microisolates in South Tyrol (MICROS): study design and epidemiological perspectives. BMC Med Genet 8, 29 (2007).
55. Penninx, B.W. et al. The Netherlands Study of Depression and Anxiety (NESDA): rationale, objectives and methods. International journal of methods in psychiatric research 17, 121-40 (2008).
56. Sullivan, P.F. et al. Genome-wide association for major depressive disorder: a possible role for the presynaptic protein piccolo. Molecular psychiatry 14, 359-75 (2009).
57. Igl, W., Johansson, A. & Gyllensten, U. The Northern Swedish Population Health Study (NSPHS)--a paradigmatic study in a rural population combining community health and basic research. Rural Remote Health 10, 1363 (2010).
58. McQuillan, R. et al. Runs of homozygosity in European populations. Am J Hum Genet 83, 359-72 (2008).
59. Hillege, H.L. et al. Urinary albumin excretion predicts cardiovascular and noncardiovascular mortality in general population. Circulation 106, 1777-82 (2002).
60. Mostert, J.P. et al. Serum uric acid levels and leukocyte nitric oxide production in multiple sclerosis patients outside relapses. Journal of the neurological sciences 231, 41-4 (2005).
61. Broadbent, H.M. et al. Susceptibility to coronary artery disease and diabetes is encoded by distinct, tightly linked SNPs in the ANRIL locus on chromosome 9p. Human molecular genetics 17, 806-14 (2008).

Nature Genetics doi:10/1038/ng.2500

62. Hofman, A., Grobbee, D.E., de Jong, P.T. & van den Ouweland, F.A. Determinants of disease and disability in the elderly: the Rotterdam Elderly Study. European journal of epidemiology 7, 403-22 (1991).
63. Hofman, A. et al. The Rotterdam Study: 2010 objectives and design update. European journal of epidemiology 24, 553-72 (2009).
64. Pilia, G. et al. Heritability of cardiovascular and personality traits in 6,148 Sardinians. PLoS genetics 2, e132 (2006).
65. Li, S. et al. The GLUT9 gene is associated with serum uric acid levels in Sardinia and Chianti cohorts. PLoS genetics 3, e194 (2007).
66. Sanna, S. et al. Common variants in the GDF5-UQCC region are associated with variation in human height. Nature genetics 40, 198-203 (2008).
67. John, U. et al. Study of Health In Pomerania (SHIP): a health examination survey in an east German region: objectives and design. Sozial- und Praventivmedizin 46, 186-94 (2001).
68. Volzke, H. et al. Cohort Profile: The Study of Health in Pomerania. International journal of epidemiology 40, 294-307 (2011).
69. Tenesa, A. et al. Genome-wide association scan identifies a colorectal cancer susceptibility locus on 11q23 and replicates risk loci at 8q24 and 18q21. Nat Genet 40, 631-7 (2008).
70. Tonjes, A. et al. Genetic variation in GPR133 is associated with height: genome wide association study in the self-contained population of Sorbs. Human molecular genetics 18, 4662-8 (2009).
71. Tonjes, A. et al. Association of FTO variants with BMI and fat mass in the self-contained population of Sorbs in Germany. European journal of human genetics : EJHG 18, 104-10 (2010).
72. Veeramah, K.R. et al. Genetic variation in the Sorbs of eastern Germany in the context of broader European genetic diversity. Eur J Hum Genet 19, 995-1001 (2011).
73. Moayyeri, A., Hammond, C.J., Valdes, A.M. & Spector, T.D. Cohort Profile: TwinsUK and Healthy Ageing Twin Study. International journal of epidemiology (2012).
74. Ridker, P.M. et al. Rationale, design, and methodology of the Women's Genome Health Study: a genome-wide association study of more than 25,000 initially healthy american women. Clinical chemistry 54, 249-55 (2008).
75. Raitakari, O.T. et al. Cohort profile: the cardiovascular risk in Young Finns Study. International journal of epidemiology 37, 1220-6 (2008).
76. Lucae, S. et al. P2RX7, a gene coding for a purinergic ligand-gated ion channel, is associated with major depressive disorder. Hum Mol Genet 15, 2438-45 (2006).
77. Kloiber, S. et al. Variations in tryptophan hydroxylase 2 linked to decreased serotonergic activity are associated with elevated risk for metabolic syndrome in depression. Mol Psychiatry 15, 736-47 (2010).
78. Kohli, M.A. et al. The neuronal transporter gene SLC6A15 confers risk to major depression. Neuron 70, 252-65 (2011).
79. Zeller, T. et al. Genetics and beyond--the transcriptome of human monocytes and disease susceptibility. PLoS One 5, e10693 (2010).
80. Wild, P.S. et al. Distribution and categorization of left ventricular measurements in the general population: results from the population-based Gutenberg Heart Study. Circulation. Cardiovascular imaging 3, 604-13 (2010).
81. Wild, P.S. et al. A genome-wide association study identifies LIPA as a susceptibility gene for coronary artery disease. Circulation. Cardiovascular genetics 4, 403-12 (2011).
82. McEvoy, M. et al. Cohort profile: The Hunter Community Study. International journal of epidemiology 39, 1452-63 (2010).
83. Portas, L. et al. History, geography and population structure influence the distribution and heritability of blood and anthropometric quantitative traits in nine Sardinian genetic isolates. Genetics research 92, 199-208 (2010).

Nature Genetics doi:10/1038/ng.2500

84. Biino, G. et al. Genetic architecture of hand quantitative ultrasound measures: a population-based study in a Sardinian genetic isolate. Bone 46, 1197-203 (2010).
85. Tore, S. et al. Application of a new method for GWAS in a related case/control sample with known pedigree structure: identification of new loci for nephrolithiasis. PLoS genetics 7, e1001281 (2011).
86. Martin, B.W. et al. SAPALDIA: methods and participation in the cross-sectional part of the Swiss Study on Air Pollution and Lung Diseases in Adults. Sozial- und Praventivmedizin 42, 67-84 (1997).
87. Ackermann-Liebrich, U. et al. Follow-up of the Swiss Cohort Study on Air Pollution and Lung Diseases in Adults (SAPALDIA 2) 1991-2003: methods and characterization of participants. Sozial- und Praventivmedizin 50, 245-63 (2005).
88. Org, E. et al. HYPEST study: profile of hypertensive patients in Estonia. BMC cardiovascular disorders 11, 55 (2011).
89. Org, E. et al. Genome-wide scan identifies CDH13 as a novel susceptibility locus contributing to blood pressure determination in two European populations. Hum Mol Genet 18, 2288-96 (2009).
90. Juhanson, P. et al. N-acetyltransferase 8, a positional candidate for blood pressure and renal regulation: resequencing, association and in silico study. BMC Med Genet 9, 25 (2008).
91. Pistis, G. et al. High differentiation among eight villages in a secluded area of Sardinia revealed by genome-wide high density SNPs analysis. PLoS One 4, e4654 (2009).
92. Bochud, M. et al. Association between white-coat effect and blunted dipping of nocturnal blood pressure. Am J Hypertens 22, 1054-61 (2009).
93. Choi, H.K., Atkinson, K., Karlson, E.W., Willett, W. & Curhan, G. Purine-rich foods, dairy and protein intake, and the risk of gout in men. The New England journal of medicine 350, 1093-103 (2004).
94. Choi, H.K., Atkinson, K., Karlson, E.W., Willett, W. & Curhan, G. Alcohol intake and risk of incident gout in men: a prospective study. Lancet 363, 1277-81 (2004).
95. Choi, H.K. & Curhan, G. Soft drinks, fructose consumption, and the risk of gout in men: prospective cohort study. BMJ 336, 309-12 (2008).
96. Choi, H.K., Willett, W. & Curhan, G. Fructose-rich beverages and risk of gout in women. JAMA : the journal of the American Medical Association 304, 2270-8 (2010).
97. Choi, H.K. & Curhan, G. Coffee consumption and risk of incident gout in women: the Nurses' Health Study. The American journal of clinical nutrition 92, 922-7 (2010).
98. Chambers, J.C. et al. Common genetic variation near MC4R is associated with waist circumference and insulin resistance. Nature genetics 40, 716-8 (2008).
99. Taylor, H.A., Jr. et al. Toward resolution of cardiovascular health disparities in African Americans: design and methods of the Jackson Heart Study. Ethn Dis 15, S6-4-17 (2005).
100. Fuqua, S.R. et al. Recruiting African-American research participation in the Jackson Heart Study: methods, response rates, and sample description. Ethn Dis 15, S6-18-29 (2005).
101. Nakamura, Y. The BioBank Japan Project. Clinical advances in hematology & oncology : H&O 5, 696-7 (2007).
102. Kamatani, Y. et al. Genome-wide association study of hematological and biochemical traits in a Japanese population. Nature genetics 42, 210-5 (2010).
103. Okada, Y. et al. Genome-wide association study for C-reactive protein levels identified pleiotropic associations in the IL6 locus. Human molecular genetics 20, 1224-31 (2011).
104. Short, K.M. & Cox, T.C. Subclassification of the RBCC/TRIM superfamily reveals a novel motif necessary for microtubule binding. The Journal of biological chemistry 281, 8970-80 (2006).
105. Sagen, J.V. et al. From clinicogenetic studies of maturity-onset diabetes of the young to unraveling complex mechanisms of glucokinase regulation. Diabetes 55, 1713-22 (2006).

Nature Genetics doi:10/1038/ng.2500

106. Gloyn, A.L. et al. Insights into the structure and regulation of glucokinase from a novel mutation (V62M), which causes maturity-onset diabetes of the young. The Journal of biological chemistry 280, 14105-13 (2005).
107. Hoggard, N. et al. Inhibin betaB expression in murine adipose tissue and its regulation by leptin, insulin and dexamethasone. Journal of molecular endocrinology 43, 171-7 (2009).
108. Magnusson, B., Svensson, P.A., Carlsson, L.M. & Sjoholm, K. Activin B inhibits lipolysis in 3T3-L1 adipocytes. Biochemical and biophysical research communications 395, 373-6 (2010).
109. Gersch, R.P. & Hadjiargyrou, M. Mustn1 is expressed during chondrogenesis and is necessary for chondrocyte proliferation and differentiation in vitro. Bone 45, 330-8 (2009).
110. Gersch, R.P. et al. Mustn1 is essential for craniofacial chondrogenesis during Xenopus development. Gene expression patterns : GEP (2012).
111. Caulfield, M.J. et al. SLC2A9 is a high-capacity urate transporter in humans. PLoS medicine 5, e197 (2008).
112. Vitart, V. et al. SLC2A9 is a newly identified urate transporter influencing serum urate concentration, urate excretion and gout. Nature genetics 40, 437-42 (2008).
113. Anzai, N. et al. Plasma urate level is directly regulated by a voltage-driven urate efflux transporter URATv1 (SLC2A9) in humans. The Journal of biological chemistry 283, 26834-8 (2008).
114. Matsuo, H. et al. Mutations in glucose transporter 9 gene SLC2A9 cause renal hypouricemia. American journal of human genetics 83, 744-51 (2008).
115. Woodward, O.M. et al. Identification of a urate transporter, ABCG2, with a common functional polymorphism causing gout. Proc Natl Acad Sci U S A 106, 10338-42 (2009).
116. Matsuo, H. et al. Common defects of ABCG2, a high-capacity urate exporter, cause gout: a function-based genetic analysis in a Japanese population. Science translational medicine 1, 5ra11 (2009).
117. Wang, P. et al. Human TMEM174 that is highly expressed in kidney tissue activates AP-1 and promotes cell proliferation. Biochemical and biophysical research communications 394, 993-9 (2010).
118. Miyamoto, K. et al. Cloning and functional expression of a Na(+)-dependent phosphate co-transporter from human kidney: cDNA cloning and functional expression. The Biochemical journal 305 (Pt 1), 81-5 (1995).
119. Reimer, R.J. & Edwards, R.H. Organic anion transport is the primary function of the SLC17/type I phosphate transporter family. Pflugers Archiv : European journal of physiology 447, 629-35 (2004).
120. Iharada, M. et al. Type 1 sodium-dependent phosphate transporter (SLC17A1 Protein) is a Cl(-)-dependent urate exporter. The Journal of biological chemistry 285, 26107-13 (2010).
121. Biber, J., Custer, M., Werner, A., Kaissling, B. & Murer, H. Localization of NaPi-1, a Na/Pi cotransporter, in rabbit kidney proximal tubules. II. Localization by immunohistochemistry. Pflugers Archiv : European journal of physiology 424, 210-5 (1993).
122. Shirwany, N.A. & Zou, M.H. AMPK in cardiovascular health and disease. Acta pharmacologica Sinica 31, 1075-84 (2010).
123. Olsen, H.S., Cepeda, M.A., Zhang, Q.Q., Rosen, C.A. & Vozzolo, B.L. Human stanniocalcin: a possible hormonal regulator of mineral metabolism. Proceedings of the National Academy of Sciences of the United States of America 93, 1792-6 (1996).
124. Gerdin, A.K. et al. Phenotypic screening of hepatocyte nuclear factor (HNF) 4-gamma receptor knockout mice. Biochemical and biophysical research communications 349, 825-32 (2006).
125. Kolz, M. et al. Meta-analysis of 28,141 individuals identifies common variants within five new loci that influence uric acid concentrations. PLoS genetics 5, e1000504 (2009).

Nature Genetics doi:10/1038/ng.2500

126. Suhre, K. et al. Human metabolic individuality in biomedical and pharmaceutical research. Nature 477, 54-60 (2011).
127. Weidemann, M.J. & Krebs, H.A. Acceleration of gluconeogenesis from propionate by DL-carnitine in the rat kidney cortex. The Biochemical journal 111, 69-81 (1969).
128. Yang, Q. et al. Multiple genetic loci influence serum urate levels and their relationship with gout and cardiovascular disease risk factors. Circ Cardiovasc Genet 3, 523-30 (2010).
129. Missler, M. & Sudhof, T.C. Neurexins: three genes and 1001 products. Trends in genetics : TIG 14, 20-6 (1998).
130. Enomoto, A. et al. Molecular identification of a renal urate anion exchanger that regulates blood urate levels. Nature 417, 447-52 (2002).
131. Dai, X. et al. The ovo gene required for cuticle formation and oogenesis in flies is involved in hair formation and spermatogenesis in mice. Genes & development 12, 3452-63 (1998).
132. Katoh, M. Molecular cloning and characterization of MFRP, a novel gene encoding a membrane-type Frizzled-related protein. Biochemical and biophysical research communications 282, 116-23 (2001).
133. Cross, H.E. & Yoder, F. Familial nanophthalmos. American journal of ophthalmology 81, 300-6 (1976).
134. Sundin, O.H. et al. Extreme hyperopia is the result of null mutations in MFRP, which encodes a Frizzled-related protein. Proceedings of the National Academy of Sciences of the United States of America 102, 9553-8 (2005).
135. Ayala-Ramirez, R. et al. A new autosomal recessive syndrome consisting of posterior microphthalmos, retinitis pigmentosa, foveoschisis, and optic disc drusen is caused by a MFRP gene mutation. Molecular vision 12, 1483-9 (2006).
136. Gi, H.t., Neidhardt, H., Schneider, C. & Pohl, J. Cloning of a new member of the TGF-beta family: a putative new activin beta C chain. Biochemical and biophysical research communications 206, 608-13 (1995).
137. Hashimoto, O. et al. cDNA cloning and expression of human activin betaE subunit. Molecular and cellular endocrinology 194, 117-22 (2002).
138. Ronimus, R.S. & Morgan, H.W. Cloning and biochemical characterization of a novel mouse ADP-dependent glucokinase. Biochemical and biophysical research communications 315, 652-8 (2004).
139. Seghatoleslam, A. et al. Analysis of a novel human gene, LOC92912, over-expressed in hypopharyngeal tumours. Biochemical and biophysical research communications 339, 422-9 (2006).
140. Harari, D. et al. Neuregulin-4: a novel growth factor that acts through the ErbB-4 receptor tyrosine kinase. Oncogene 18, 2681-9 (1999).
141. Bonafe, M. et al. Polymorphic variants of insulin-like growth factor I (IGF-I) receptor and phosphoinositide 3-kinase genes affect IGF-I plasma levels and human longevity: cues for an evolutionarily conserved mechanism of life span control. The Journal of clinical endocrinology and metabolism 88, 3299-304 (2003).
142. Miyakawa, H., Woo, S.K., Dahl, S.C., Handler, J.S. & Kwon, H.M. Tonicity-responsive enhancer binding protein, a rel-like protein that stimulates transcription in response to hypertonicity. Proceedings of the National Academy of Sciences of the United States of America 96, 2538-42 (1999).
143. Kanamaru, M. et al. Aldose reductase inhibitory and uricosuric activities of FK366 in healthy volunteers. Journal of clinical pharmacology 33, 1122-31 (1993).
144. Lopez-Rodriguez, C. et al. Loss of NFAT5 results in renal atrophy and lack of tonicity-responsive gene expression. Proceedings of the National Academy of Sciences of the United States of America 101, 2392-7 (2004).

Nature Genetics doi:10/1038/ng.2500

145. MacLean, H.E et al. Absence of transcription factor c-maf causes abnormal terminal differentiation of hypertrophic chondrocytes during endochondral bone development. Developmental biology 262, 51-63 (2003).
146. Teumer, A. et al. Genome-wide association study identifies four genetic loci associated with thyroid volume and goiter risk. American journal of human genetics 88, 664-73 (2011).
147. Gururaj, A.E. et al. MTA1, a transcriptional activator of breast cancer amplified sequence 3. Proceedings of the National Academy of Sciences of the United States of America 103, 6670-5 (2006).
148. Ishizuka, T. et al. The human phosphoribosylpyrophosphate synthetase-associated protein 39 gene (PRPSAP1) is located in the chromosome region 17q24-q25. Genomics 33, 332-4 (1996).
149. Roessler, B.J. et al. Human X-linked phosphoribosylpyrophosphate synthetase superactivity is associated with distinct point mutations in the PRPS1 gene. The Journal of biological chemistry 268, 26476-81 (1993).
150. Oleinikov, A.V., Zhao, J. & Makker, S.P. Cytosolic adaptor protein Dab2 is an intracellular ligand of endocytic receptor gp600/megalin. The Biochemical journal 347 Pt 3, 613-21 (2000).
151. Li, J., Mahajan, A. & Tsai, M.D. Ankyrin repeat: a unique motif mediating protein-protein interactions. Biochemistry 45, 15168-78 (2006).
152. Lang, H.L. et al. A functional and structural basis for TCR cross-reactivity in multiple sclerosis. Nature immunology 3, 940-3 (2002).
153. Jin, Y. et al. Genome-wide analysis identifies a quantitative trait locus in the MHC class II region associated with generalized vitiligo age of onset. The Journal of investigative dermatology 131, 1308-12 (2011).
154. Clancy, R.M. et al. Identification of candidate loci at 6p21 and 21q22 in a genome-wide association study of cardiac manifestations of neonatal lupus. Arthritis and rheumatism 62, 3415-24 (2010).
155. Feng, B.J. et al. Multiple Loci within the major histocompatibility complex confer risk of psoriasis. PLoS genetics 5, e1000606 (2009).
156. Sweetman, W.A. et al. SSCP and segregation analysis of the human type X collagen gene (COL10A1) in heritable forms of chondrodysplasia. American journal of human genetics 51, 841-9 (1992).
157. Lamas, J.R. et al. Large-scale gene expression in bone marrow mesenchymal stem cells: a putative role for COL10A1 in osteoarthritis. Annals of the rheumatic diseases 69, 1880-5 (2010).
158. Courtois, G., Morgan, J.G., Campbell, L.A., Fourel, G. & Crabtree, G.R. Interaction of a liver-specific nuclear factor with the fibrinogen and alpha 1-antitrypsin promoters. Science 238, 688-92 (1987).
159. Lauc, G. et al. Genomics meets glycomics-the first GWAS study of human N-Glycome identifies HNF1alpha as a master regulator of plasma protein fucosylation. PLoS genetics 6, e1001256 (2010).
160. Cheret, C., Doyen, A., Yaniv, M. & Pontoglio, M. Hepatocyte nuclear factor 1 alpha controls renal expression of the Npt1-Npt4 anionic transporter locus. Journal of molecular biology 322, 929-41 (2002).
161. Sekine, T. et al. Identification of multispecific organic anion transporter 2 expressed predominantly in the liver. FEBS letters 429, 179-82 (1998).
162. Sato, M. et al. Renal secretion of uric acid by organic anion transporter 2 (OAT2/SLC22A7) in human. Biol Pharm Bull 33, 498-503 (2010).
163. Hirai, T. & Chida, K. Protein kinase Czeta (PKCzeta): activation mechanisms and cellular functions. Journal of biochemistry 133, 1-7 (2003).

Nature Genetics doi:10/1038/ng.2500

164. Bandyopadhyay, G., Standaert, M.L., Galloway, L., Moscat, J. & Farese, R.V. Evidence for involvement of protein kinase C (PKC)-zeta and noninvolvement of diacylglycerol-sensitive PKCs in insulin-stimulated glucose transport in L6 myotubes. Endocrinology 138, 4721-31 (1997).
165. Bandyopadhyay, G. et al. PKC-zeta mediates insulin effects on glucose transport in cultured preadipocyte-derived human adipocytes. The Journal of clinical endocrinology and metabolism 87, 716-23 (2002).
166. Pastalkova, E. et al. Storage of spatial information by the maintenance mechanism of LTP. Science 313, 1141-4 (2006).
167. Barros, S.A. et al. Activation of protein kinase Czeta increases OAT1 (SLC22A6)- and OAT3 (SLC22A8)-mediated transport. The Journal of biological chemistry 284, 2672-9 (2009).
168. Bakhiya, A., Bahn, A., Burckhardt, G. & Wolff, N. Human organic anion transporter 3 (hOAT3) can operate as an exchanger and mediate secretory urate flux. Cellular physiology and biochemistry : international journal of experimental cellular physiology, biochemistry, and pharmacology 13, 249-56 (2003).
169. Semenza, G.L. & Wang, G.L. A nuclear factor induced by hypoxia via de novo protein synthesis binds to the human erythropoietin gene enhancer at a site required for transcriptional activation. Molecular and cellular biology 12, 5447-54 (1992).
170. Forsythe, J.A. et al. Activation of vascular endothelial growth factor gene transcription by hypoxia-inducible factor 1. Molecular and cellular biology 16, 4604-13 (1996).
171. Jung, F., Palmer, L.A., Zhou, N. & Johns, R.A. Hypoxic regulation of inducible nitric oxide synthase via hypoxia inducible factor-1 in cardiac myocytes. Circulation research 86, 319-25 (2000).
172. Semenza, G.L., Roth, P.H., Fang, H.M. & Wang, G.L. Transcriptional regulation of genes encoding glycolytic enzymes by hypoxia-inducible factor 1. The Journal of biological chemistry 269, 23757-63 (1994).
173. Krishnamurthy, P. & Schuetz, J.D. The ABC transporter Abcg2/Bcrp: role in hypoxia mediated survival. Biometals : an international journal on the role of metal ions in biology, biochemistry, and medicine 18, 349-58 (2005).
174. Kietzmann, T., Krones-Herzig, A. & Jungermann, K. Signaling cross-talk between hypoxia and glucose via hypoxia-inducible factor 1 and glucose response elements. Biochemical pharmacology 64, 903-11 (2002).
175. Webster, J.A. et al. Genetic control of human brain transcript expression in Alzheimer disease. American journal of human genetics 84, 445-58 (2009).
176. Abdullah, H.I., Pedraza, P.L., McGiff, J.C. & Ferreri, N.R. Calcium-sensing receptor signaling pathways in medullary thick ascending limb cells mediate COX-2-derived PGE2 production: functional significance. American journal of physiology. Renal physiology 295, F1082-9 (2008).
177. Tsuchida, K. et al. Activin isoforms signal through type I receptor serine/threonine kinase ALK7. Molecular and cellular endocrinology 220, 59-65 (2004).
178. Watanabe, R. Activin receptor-like kinase and the insulin gene. Vitamins and hormones 85, 1-27 (2011).
179. Margariti, A. et al. Histone deacetylase 7 controls endothelial cell growth through modulation of beta-catenin. Circulation research 106, 1202-11 (2010).
180. Wang, S. et al. Control of endothelial cell proliferation and migration by VEGF signaling to histone deacetylase 7. Proceedings of the National Academy of Sciences of the United States of America 105, 7738-43 (2008).
181. Tin, A. et al. Genome-wide association study for serum urate concentrations and gout among African Americans identifies genomic risk loci and a novel URAT1 loss-of-function allele. Hum Mol Genet 20, 4056-68 (2011).
182. Li, Y., Willer, C.J., Ding, J., Scheet, P. & Abecasis, G.R. MaCH: using sequence and genotype data to estimate haplotypes and unobserved genotypes. Genetic epidemiology 34, 816-34 (2010).

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