Human Molecular Genetics, 2011, Vol. 20, No. 20 **4056–4068**
doi:10.1093/hmg/ddr307
Advance Access published on July 18, 2011

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

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Received March 15, 2011; Revised May 25, 2011; Accepted July 11, 2011

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Serum urate concentrations are highly heritable and elevated serum urate is a key risk factor for gout. Genome-wide association studies (GWAS) of serum urate in African American (AA) populations are lacking. We conducted a meta-analysis of GWAS of serum urate levels and gout among 5820 AA and a large candidate gene study among 6890 AA and 21 708 participants of European ancestry (EA) within the Candidate Gene Association Resource Consortium. Findings were tested for replication among 1996 independent AA individuals, and evaluated for their association among 28 283 EA participants of the CHARGE Consortium. Functional studies were conducted using ^{14}C-urate transport assays in mammalian Chinese hamster ovary cells. In the discovery GWAS of serum urate, three loci achieved genome-wide significance ($P < 5.0 \times 10^{-8}$): a novel locus near *SGK1*/*SLC2A12* on chromosome 6 (rs9321453, $P = 1.0 \times 10^{-9}$), and two loci previously identified in EA participants, *SLC2A9* ($P = 3.8 \times 10^{-32}$) and *SLC22A12* ($P = 2.1 \times 10^{-10}$). A novel rare non-synonymous variant of large effect size in *SLC22A12*, rs12800450 (minor allele frequency 0.01, G65W), was identified and replicated (beta −1.19 mg/dl, $P = 2.7 \times 10^{-16}$). ^{14}C-urate transport assays showed reduced urate transport for the G65W URAT1 mutant. Finally, in analyses of 11 loci previously associated with serum urate in EA individuals, 10 of 11 lead single-nucleotide polymorphisms showed direction-consistent association with urate among AA. In summary, we identified and replicated one novel locus in association with serum urate levels and experimentally characterize the novel G65W variant in URAT1 as a functional allele. Our data support the importance of multi-ethnic GWAS in the identification of novel risk loci as well as functional variants.

INTRODUCTION

Uric acid is the breakdown product of purines in humans, who lack uricase. An elevated level of serum urate, hyperuricemia, is a key risk factor for gout (1). Gout is the most common inflammatory arthritis in men, with a prevalence of 1–2% (2). Serum urate levels are highly heritable (3). Several Mendelian syndromes featuring hypo- or hyperuricemia and gout are known [OMIM ID #220150 (*SLC22A12*), #300322 (*HPRT*), #300661 (*PRPS1*), #612076 (*SLC2A9*)]. It is therefore of interest to identify both genetic variants that increase and those that decrease serum urate levels to obtain a complete understanding of an individual's predisposition to hyperuricemia and gout. Genome-wide association studies (GWAS) have identified common variants that are associated with serum urate levels and gout among individuals of European ancestry (EA) (4–10). Follow-up projects discovered that the proteins encoded by two of the identified genes, *SLC2A9* (7,11,12) and *ABCG2* (13–14), function as urate transporters, furthering our knowledge of urate metabolism in humans.

Despite this progress, GWAS for common genetic risk variants for hyperuricemia and gout have only been reported from EA study participants as well as a Japanese study population (15). Additionally, the reported higher cumulative incidence of gout among African American (AA) men compared with EA men (10.9 versus 5.8%) (16) as well as the reported higher prevalence of gout among middle-aged AA compared with EA study participants (8.8 versus 5.4%) (8) motivates the search for genetic risk variants in AA populations.

Thus, the objectives of this work were to identify novel variants influencing serum urate levels and gout risk among AA participants of the Candidate Gene Association Resource (CARe) Consortium (17), a consortium of nine studies with ~8000 AA participants with information on ~2.5 million genotyped and imputed single-nucleotide polymorphisms (SNPs) as well as ~40 000 EA and AA participants with information on 50 000 genotyped SNPs with dense coverage in cardiovascular disease and inflammation pathway candidate genes across ~2000 loci (IBC array). Because of the strong observational link between serum urate concentrations and cardiovascular disease and its risk factors (18) and the link between gout and inflammation (19), genotyping of the IBC chip may provide information beyond that obtained from a genome-wide SNP platform. Urate transport assays were conducted to assess functionality of novel rare non-synonymous variants in urate transporters.

RESULTS

Study sample characteristics by genotyping array are shown in Table 1. For the GWAS of serum urate, the overall sample size was 5820 AA participants [mean serum urate levels 5.8 mg/dl (SD 1.7)]. The GWAS of gout were conducted among 2831 individuals (177 gout cases). For the analysis of SNPs on the IBC chip, 6890 AA and 21 708 EA participants contributed information; sample size information for gout and mean urate levels are reported in Table 1. Within all AA study samples, median European ancestry ranged from 15.2 to 20.5% (Table 1).

GWAS for serum urate concentrations and gout among AA participants

Figure 1 presents a plot of $-\log_{10}(P\text{-values})$ by genomic position for the GWAS of serum urate among AA participants. The quantile–quantile plots are shown in Supplementary Material, Figure S1 for serum urate with and without genomic regions known to contain urate-associated genes among EA populations (A, B) and for gout (C). Significant associations ($P < 5.0 \times 10^{-8}$) were observed for SNPs in one novel region on chromosome 6 (closest genes *SGK1* and *SLC2A12*) as well as two genomic regions previously reported among EA participants (*SLC2A9* and *SLC22A12*; *P*-value range 2.1×10^{-10} to 3.8×10^{-32}; Table 2). Regional association plots of the novel region providing information on both

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Table 1. Study sample characteristics in the individual studies, CARe

Study	Sample size (uric acid/gout)	Median European Ancestry, % (25, 75 percentile)[a]	Age in years (SD)[b]	Women % (*n*)[a]	UA, mg/dl (SD)	Gout % (*n*)
Affy 6.0—African Americans						
ARIC	2749/1908	15.3 (10.7, 22.1)	53 (5.8)	62.9 (1728)	6.28 (1.66)	8.33 (159)
CARDIA	937/923	16.8 (12.4, 23.4)	24 (3.8)	60.9 (571)	5.12 (1.34)	1.95 (18)
JHS	2134/NA	15.7 (11.8, 21.1)	50 (12.1)	60.8 (1297)	5.45 (1.69)	NA
Total	5820/2831	15.7 (11.4, 21.9)	47 (13.3)	61.8 (3596)	5.79 (1.69)	6.25 (177)
IBC chip—African Americans						
ARIC	2927/2010	15.2 (10.5, 22.8)	53 (5.8)	62.9 (1840)	6.30 (1.68)	8.66 (174)
CARDIA	1268/1254	16.8 (11.8, 23.7)	24 (3.8)	58.9 (747)	5.12 (1.38)	1.83 (23)
CHS	727/NA	20.5 (12.4, 32.7)	73 (5.7)	62.9 (457)	5.79 (1.63)	NA
JHS	2027/NA	15.9 (11.5, 21.9)	50 (12.0)	60.6 (1229)	5.43 (1.68)	NA
Total	6890/3264	16.2 (11.2, 23.3)	49 (15.5)	61.5 (4273)	5.78 (1.69)	6.04 (197)
IBC chip—European Americans						
ARIC	9581/7719	NA	54 (5.7)	53.5 (5128)	5.93 (1.50)	5.22 (403)
CARDIA	1430/1411	NA	26 (3.4)	53.3 (762)	5.34 (1.37)	1.28 (18)
CHS	3938/NA	NA	73 (5.6)	56.1 (2208)	5.67 (1.52)	NA
FHS	6759/6757	NA	38 (9.6)	53.4 (3607)	5.42 (1.47)	2.19 (148)
Total	21708/15887	NA	51 (15.4)	53.9 (11705)	5.69 (1.50)	3.58 (569)
Replication—African Americans						
HANDLS	989/NA	16.1 (11.2, 22.0)	48 (9.0)	55.7 (551)	5.55 (1.65)	NA
HUFS	1007/NA	19.7 (14.3, 26.9)	48 (13.2)	58.9 (593)	5.53 (1.64)	NA
Total	1996/NA					

[a]Summary statistics based on uric acid samples and similar to those from the gout samples.
[b]Age of serum urate data collection.

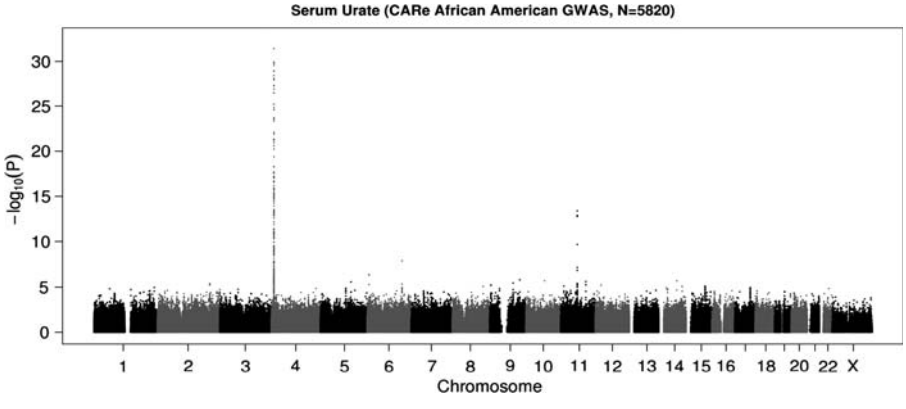

Figure 1. $-\log_{10}$(*P*-value) by genomic position plot for the GWAS of serum urate among 5820 AA participants.

r^2 and D' as measures of linkage disequilibrium (LD) are presented in Figure 2. A search of publicly available expression data sets (http://eqtl.uchicago.edu/cgi-bin/gbrowse/eqtl/) did not provide evidence that the novel SNP rs9321453 was associated with the transcription of either *SGK1* or *SLC2A12* in any of the 13 data sets queried.

At the known loci *SLC2A9* and *SLC22A12*, multiple signals in low LD were observed (rs13129697 and rs7663032 with $r^2 = 0.31$, *SLC2A9*; rs606458 and rs493573 with $r^2 = 0.02$, *SLC22A12*). Based on multivariable regression analyses in the ARIC AA sample ($n = 2749$) that included the SNPs simultaneously, the two common genome-wide significant SNPs in *SLC2A9* accounted for 3.2% of the serum urate variance (separately 2.6 and 2.3%). The three genome-wide significant SNPs in the *SLC22A12* region were moderately correlated with r^2 ranging from 0.02 to 0.45. Together, the two rare and one common SNP accounted for 1.2% of the serum urate variance (separately 0.5 and 0.7% for the two rare variants, rs12800450 and rs493573, respectively, and 0.6% for rs606458).

Two significant SNPs in the *SLC22A12* region were coding variants of low minor allele frequency: non-synonymous rs12800450 [(G65W), minor allele frequency (MAF) 0.01, $P = 4.0 \times 10^{-14}$] in *SLC22A12*, which encodes the known urate transporter URAT1, and synonymous rs493573 in nearby *MAP4K2* [(A806A), MAF 0.03, $P = 1.3 \times 10^{-13}$]. The two variants were correlated ($r^2 = 0.45$, $D' = 1$). The effect of the variants on serum urate levels was ~6- to 10-fold larger than the one observed for more common variants in *SLC22A12* (Table 2). No genome-wide significant associations were observed in GWAS of gout.

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Table 2. Loci in AA from GWAS: SNP association with uric acid levels

SNP ID	Chr	Position (b36)	Genes within 60 kb	SNP function	Coded allele frequency	Coded allele	Beta (mg/dl)	SE	Discovery *P*-value	Replication beta	Replication *P*-value	Meta-analysis beta	Meta-analysis *P*-value
Novel Loci													
rs9321453	6	134815247	NA	Intergenic	0.42	T	0.15	0.03	1.4×10^{-08}	0.11	2.4×10^{-02}	0.14	1.0×10^{-09}
Known Loci													
rs13129697	4	9536065	*SLC2A9*	Intronic	0.42	T	0.32	0.03	3.8×10^{-32}	[a]	[a]	[a]	[a]
rs7663032	4	9602936	*SLC2A9*	Intronic	0.67	T	0.32	0.03	1.2×10^{-30}	[a]	[a]	[a]	[a]
rs12800450	11	64115797	*SLC22A12*	Non-synonymous coding	0.01	T	−1.21	0.16	4.0×10^{-14}	−1.08	5.0×10^{-03}	−1.19	2.7×10^{-16}
rs606458	11	64302967	*MEN1;SF1;MAP4K2; PYGM;RASGRP2; CDC42BPG;NRXN2*	Intergenic	0.35	T	−0.21	0.03	2.1×10^{-10}	−0.11	3.9×10^{-02}	−0.18	5.5×10^{-11}
rs493573	11	64313630	*MAP4K2*	Synonymous coding	0.03	T	−0.81	0.11	1.3×10^{-13}	−0.74	6.9×10^{-05}	−0.80	1.9×10^{-17}

[a]Not sent for replication due to LD ($r^2 > 0.2$) with reported index SNP according to the HapMap CEU and YRI data.

A total of 1996 AA participants from two independent studies, 989 participants from the HANDLS study and 1007 participants from HUFS study, were available for replication of novel findings. The SNP with the lowest *P*-value at the novel locus on chromosome 6, rs9321453, was of comparable effect size in the replication samples and showed evidence for nominal independent replication in the AA replication samples (*P*-replication = 0.024) as well as overall replication (*P*-combined = 1.0×10^{-9}, Table 2). Study-specific results for the replication studies are presented in Supplementary Material, Table S1. The two low-frequency coding variants identified in the GWAS of serum urate also showed evidence for independent replication among the AA replication samples (rs12800450: *P*-replication = 0.005; rs493573, *P*-replication = 6.9×10^{-5}) as well as overall replication.

We further evaluated SNPs identified in our AA samples for their effect among 28 283 EA participants of the large international CHARGE Consortium (20). The novel SNP rs9321453 on chromosome 6 showed no association among EA individuals ($P = 0.82$), and the region among EA individuals is depicted in Supplementary Material, Figure S2. The common SNPs at the *SLC2A9* and *SLC22A12* loci listed in Table 2 showed highly significant association with serum urate for the same modeled allele in the CHARGE participants (*P*-value range 8.0×10^{-6} to 1.5×10^{-242}, Supplementary Material, Table S2). The low-frequency variants in the *SLC22A12* gene region discovered in our analyses were not evaluated among the CHARGE samples because the SNPs were monomorphic in all (rs493573) or some (rs12800450) of the individual studies with frequencies as low as 0.01%, making the estimates not reliable.

IBC chip analyses for serum urate and gout

Supplementary Material, Table S3 shows SNPs with significant association ($P < 2.0 \times 10^{-6}$) with serum urate and gout among the 21 708 EA participants with genotype data from the IBC cardiovascular disease candidate gene chip. There were five regions with evidence of association with serum urate (*P*-value range 8.3×10^{-8} to 1.9×10^{-44}), all of which had been reported in previous GWAS of serum urate among EA participants (4,10). For gout, the known functional variant rs2231142 in *ABCG2* showed evidence of significant association [odds ratio (OR) = 1.72 per T allele, $P = 3.1 \times 10^{-10}$]. Among 6890 AA participants, no significant associations were observed for either phenotype. Replication of findings from the IBC analyses was not sought, as there were no significant findings for the AA participants, and all the regions identified among EA participants had been reported previously.

Functional studies

Urate transport assays were performed to assess whether the G65W variant of URAT1, encoded by rs12800450 in *SLC22A12*, is a functional allele. This was the only variant selected for functional follow-up studies because of the encoded non-synonymous amino acid substitution, the large effect on serum urate per copy of the minor allele (−1.2 mg/dl), the biological plausibility of the encoded renal urate transporter URAT1 and the predicted damaging

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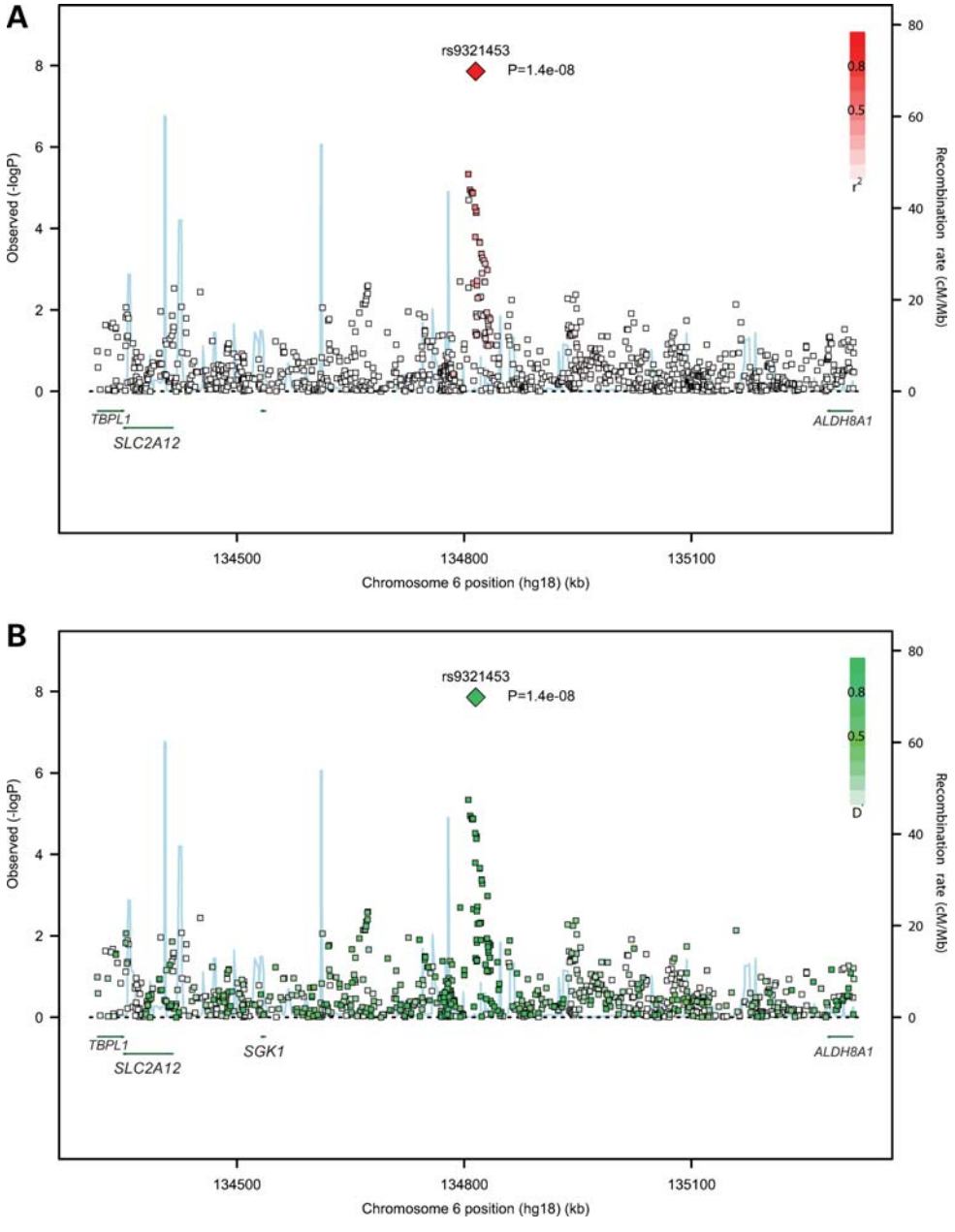

Figure 2. Regional association plots of SNPs at the novel chromosome 6 locus near *SGK1*/*SLC2A12* and their association with serum urate. The upper panel shows r^2 as a measure of LD (red), and the lower one shows D' (green).

function of the amino acid substitution (PolyPhen2: score 0.99; sensitivity: 0.64, specificity: 0.95) (21). Mammalian Chinese hamster ovary (CHO) cells transiently transfected with human G65W URAT1 exhibited significantly reduced ^{14}C-urate transport in comparison to cells expressing wild-type (WT) human URAT1 ($P < 0.001$, Fig. 3).

Association with gout for SNPs discovered for serum urate

Table 3 presents the association with gout for SNPs that show significant association with serum urate levels among CARe AA participants (GWAS) and CARe EA participants (IBC). Of the six SNPs in AA, the associations between gout and the two SNPs in *SLC2A9* were significant after correction for multiple testing [P-value $< 8.3 \times 10^{-3}$ ($=0.05/6$)], with OR of 1.4 and 1.46. In EA participants, the functional variant rs2231142 in ABCG2 is associated with gout at a genome-wide significance level as reported previously (4). For all 12 SNPs, directionally consistent effects on serum urate and gout were observed (P-binomial < 0.0001).

Interrogation of known loci associated with serum urate among AA participants

We interrogated genomic regions known to contain SNPs associated with serum urate in individuals of EA among the

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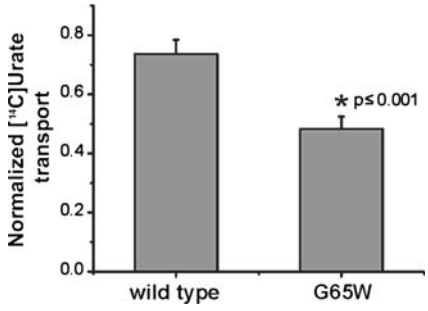

Figure 3. Urate transport in mammalian CHO cells: normalized ^{14}C urate transport rates in CHO cells transiently transfected with either the WT URAT1 or the G65W mutant ($n = 9$ for each; $\pm$SEM).

5820 AA CARe participants with GWAS data. Table 4 lists the 11 genomic regions that were investigated. For the index SNP known from studies in EA participants, 10/11 SNPs showed directionally consistent effects on serum urate for the same modeled allele among AA CARe participants (*P*-binomial = 0.0005). For six of the index SNPs at five distinct genomic regions, nominally significant *P*-values were observed among AA participants (SNPs in *PDZK1*, *SLC2A9*, *RREB1*, *SLC22A12* and *R3HDM2*; Table 4). Effect sizes of three SNPs (in *PDZK1*, *SLC22A12*, *R3HDM2*) were over 50% stronger in AA compared with EA individuals. The effect sizes of the other three SNPs (two in *SLC2A9*, one in *RREB1*) were of similar magnitude in EA and AA individuals. No significant signal was observed for the index SNP rs780094 in *GCKR*. Among EA participants, this SNP is in high LD with non-synonymous coding rs1260326 (r^2 of 0.93 in HapMap2 CEU; r^2 of 0.43 in HapMap2 YRI), which has been reported as a functional variant (22). In our AA data, there was no significant association between the rs1260326 T allele and serum urate (beta 0.0135, *P*-value 0.72, MAF 0.16).

As a second step, we interrogated the region that contained the index SNP known from EA individuals for association with serum urate among CARe AA participants (Supplementary Material, Table S4). Eight of the 11 known EA regions contained SNPs with significant associations (*P*-value range 1.1×10^{-3} to 3.8×10^{-32}). In the *GCKR* region, independent signals were observed in nearby *RBKS*, which did, however, not replicate (Supplementary Material, Table S4). Supplementary Material, Figure S3A–K shows, for each interrogated region, the AA association results; the index SNP among EA individuals is highlighted. Supplementary Material, Figure S4 shows the LD as measured by r^2 of the CEU and YRI populations for the *GCKR* region, for which LD structure and associations with serum urate differed between EA and AA individuals. Details about genotyping and quality control procedures are reported in Supplementary Material, Table S5, and imputation quality of significant SNPs in Supplementary Material, Table S6. All SNPs that attained genome-wide and IBC-wide significance are listed in Supplementary Material, Table S7.

DISCUSSION

Principal findings

In our GWAS of serum urate levels among AA individuals, we identified and replicated one novel locus, near *SGK1/*

Table 3. Association of urate loci with gout

SNP	Chr	Position (b36)	Genes within 60 kb	Coded allele	Gout beta	Gout SE	Gout OR	95% CI	*P*-value
African American Affy Loci									
rs9321453	6	134815247	NA	T	0.21	0.12	1.23	0.98, 1.55	7.16×10^{-02}
rs13129697	4	9536065	*SLC2A9*	T	0.33	0.12	1.40	1.11, 1.76	4.66×10^{-03}
rs7663032	4	9602936	*SLC2A9*	T	0.38	0.13	1.46	1.13, 1.88	3.97×10^{-03}
rs12800450	11	64115797	*SLC22A12*	T	−1.36	1.06	0.26	0.03, 2.04	1.98×10^{-01}
rs606458	11	64302967	*MEN1;SF1;MAP4K2; PYGM;RASGRP2; CDC42BPG;NRXN2*	T	−0.14	0.15	0.87	0.65, 1.16	3.44×10^{-01}
rs493573	11	64313630	*MAP4K2*	T	−1.51	0.75	0.22	0.05, 0.97	4.51×10^{-02}
European American IBC Loci									
rs1260326	2	27584444	*GCKR*	T	0.07	0.06	1.08	0.95, 1.22	2.32×10^{-01}
rs2241480	4	9684583	*WDR1, SLC2A9*	T	0.21	0.09	1.24	1.03, 1.49	2.45×10^{-02}
rs2231142	4	89271347	*ABCG2*	T	0.54	0.09	1.72	1.45, 2.03	3.13×10^{-10}
rs2051541	6	25934098	*SLC17A1 / SLC17A3*	A	−0.13	0.08	0.88	0.74, 1.03	1.19×10^{-01}
rs10792443	11	64147733	*NRXN2, SLC22A11*	C	−0.14	0.10	0.87	0.71, 1.06	1.68×10^{-01}
rs11172147	12	55982944	*R3HDM2*	A	−0.20	0.09	0.82	0.69, 0.97	1.90×10^{-02}

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Table 4. Interrogation of imputed GWAS data in AA for SNPs previously identified in GWAS of urate levels in European ancestry (EA) individuals

Paper	CHR	SNP (proxy)	Position	Gene	Coded allele	Coded allele frequency in EA	Beta in EA	*P*-value in EA	Coded allele frequency in AA	Beta in AA	*P*-value in AA
Kolz (10)	1	rs12129861	144437046	*PDZK1*	A	0.46	−0.06	2.68×10^{-09}	0.39	−0.11	8.73×10^{-05}
Kolz	2	rs780094	27594741	*GCKR*	T	0.42	0.05	1.40×10^{-09}	0.18	−0.03	4.40×10^{-01}
Kolz	4	rs734553	9532102	*SLC2A9*	T	0.77	0.32	5.22×10^{-201}	0.47	0.28	2.68×10^{-24}
Delghan (8)	4	rs6449213	9603313	*SLC2A9*	C	0.18	−0.35	2.20×10^{-104}	0.14	−0.29	2.84×10^{-14}
Kolz	4	rs2231142 (rs4148155)[a]	89273941	*ABCG2*	T	0.11	0.17	3.10×10^{-26}	0.03	0.16	5.50×10^{-02}
Yang (4)	6	rs675209	7047083	*RREB1*	T	0.26	0.07	1.00×10^{-09}	0.48	0.06	4.86×10^{-02}
Kolz	6	rs742132	25715550	*LRRC16*	A	0.70	0.05	8.50×10^{-09}	0.70	0.01	6.35×10^{-01}
Kolz	6	rs1183201	25931423	*SLC17A1*, *SLC17A3*	A	0.48	−0.06	3.04×10^{-14}	0.13	−0.07	8.20×10^{-02}
Kolz	10	rs12356193	61083359	*SLC16A9*	A	0.83	0.08	1.07×10^{-08}	0.92	0.06	2.86×10^{-01}
Kolz	11	rs17300741	64088038	*SLC22A11*	A	0.51	0.06	6.68×10^{-14}	0.58	0.04	1.53×10^{-01}
Kolz	11	rs505802	64113648	*SLC22A12*	T	0.70	−0.06	2.04×10^{-09}	0.32	−0.13	5.24×10^{-06}
Yang	12	rs1106766	56095723	*R3HDM2*	T	0.23	−0.09	1.90×10^{-11}	0.09	−0.16	6.46×10^{-04}

SNPs were counted as 11 independent loci, as the r^2 between the two SNPs at the *SLC2A9* locus was 0.69 in CEU (HapMap rel 22) and the two SNPs were therefore counted as one locus.
[a]rs4148155, which has an r^2 of 1 with rs2231142, was used because rs2231142 was not available on the GWAS platform.

SLC2A12, and confirmed associations at two loci, *SLC2A9* and *SLC22A12*, previously detected among EA individuals. Using urate transport assays, we showed that the novel rare G65W variant in URAT1, encoded by rs12800450 in *SLC22A12*, is a functional allele that displays reduced urate transport capacity in mammalian cells. In 11 regions previously known to associate with serum urate among EA individuals, we observed similar associations for 10 of the lead EA SNPs in our AA cohorts, of which 6 SNPs at 5 distinct loci were significantly associated with serum urate. Differences in the allelic spectrum of genetic variants between AA and EA individuals and the greater linkage equilibrium in AA may explain the lack of significant association at the other loci.

In the context of the current literature

Our study extends findings from previous GWAS among individuals of EA by identifying one novel locus on chromosome 6 near the *SGK1* and *SLC2A12* genes. We further extend previous knowledge by identifying independent urate-associated signals in the *SLC2A9* and *SLC22A12* regions as well as rare variants in the *SLC22A12* region that was not identified in earlier studies of EA individuals or in the isolated population of the Island of Kosrae (23). More importantly, we evaluate and confirm functionality of an identified low-frequency non-synonymous coding variant in *SLC22A12*, allowing for the conclusion that the minor allele at this variant causes lower serum urate levels and consequently reduced risk of gout. This is in agreement with the knowledge of rare-inactivating mutations in the encoded protein URAT1, which can cause renal hypouricemia (OMIM #220150) (24); affected individuals display serum urate levels as low as 1 mg/dl for individuals homozygous for a loss-of-function variant (25). Recent data from the 1000 Genomes Project suggest that each individual differs from the reference human genome sequence at ~10 000 non-synonymous sites, but that only ~400 of these variants are causing premature stops, altered splicing or frame shifts (26). With the accelerated identification of rare non-synonymous coding variants, it will be increasingly important to assess experimentally whether an identified variant that causes an amino acid substitution indeed is functional.

In this GWAS of serum urate and gout among AA study participants, 10 of the 11 loci known to influence serum urate in EA individuals showed directionally consistent association for the same modeled allele in our AA samples. Six of the EA index SNPs at five distinct loci were nominally significantly associated, and although not significant among our smaller AA samples, the effects of three of the remaining index SNPs were of comparable size in the AA population. This suggests that variants at most genomic regions that influence serum urate levels in individuals of EA also contain associated variants in AA. These results are consistent with observations made for other traits, for example blood lipid-associated variants (17,27). In the *GCKR* gene region, our results do not support rs1260326 as the causal variant responsible for the association with serum urate, as no association was observed among AA participants.

Biological mechanisms

The SNP with the lowest *P*-value at the novel urate-associated locus on chromosome 6, rs9321453, is located ~134 kb upstream of the next RefSeq gene, *SGK1*. The *SGK1* gene encodes the serine/threonine protein kinase serum/glucocorticoid-regulated kinase 1 (28), which activates certain potassium, sodium and chloride channels. Another gene in the region is the neighboring *SLC2A12*, which encodes GLUT12 (29). GLUT12 is a facilitative glucose transporter that belongs to the same overall family as the known urate transporter GLUT9, encoded by *SLC2A9* (30). It is therefore an interesting candidate emerging from the extended region on chromosome 6, especially since many of the genes identified in our study encode known urate transport proteins (*ABCG2*, *SLC2A9*, *SLC22A11*, *SLC22A12*, *SLC17A1*) or regulators thereof (*PDZK1*). Although recombination hot spots separate rs9321453 from the nearby genes *SGK1* and *SLC2A12*, this SNP displays high LD measured by D' with low-frequency SNPs in the

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nearby genes based on Hapmap YRI release 22 data (Fig. 2). It is therefore conceivable that variation in these genes could give risk to the observed signal, but additional studies are needed to pinpoint the causal variant as well as to evaluate whether this locus harbors population-specific variants in AA influencing serum urate levels.

The only rare genome-wide significant non-synonymous coding variant we identified, rs12800450 in *SLC22A12*, exhibited up to 10-fold larger effects on mean urate levels compared with more common alleles in *SLC22A12*. *SLC22A12* encodes for the urate/anion exchanger URAT1, which is one of the two main urate transport proteins responsible for the reabsorption of urate from urine into blood and is localized in the apical membrane of renal proximal tubular cells (31). Although the G65W URAT1 variant displayed residual urate transport activity, the fact that each copy of the minor allele is associated with ~1.0 mg/dl lower mean serum urate levels underscores the importance of this transporter in regulating serum urate levels in humans. The reduced urate transport rates and consequently lower mean serum urate concentrations we observe for the G65W variant, together with the localization of URAT1 in the kidney, are consistent with G65W being a partial loss-of-function allele. Genetic variation contributing to each individual's serum urate levels and gout risk is a combination of urate-increasing and urate-lowering alleles. To obtain a more complete picture of the genetic risk of hyperuricemia and gout, it is therefore necessary to identify and characterize both urate-increasing and urate-lowering functional alleles, as done here.

Strengths and limitations

Strengths of our study include the large sample size of ~7000 AA individuals for the discovery analyses of serum urate, as well as the availability of independent replication cohorts of both AA and EA individuals. The genetic variants examined were genotyped on the same genome-wide array in all studies participating in the CARe Consortium, and were complemented by an additional 50 000 SNPs genotyped on a large candidate gene chip. Importantly, we were able to show through functional studies that the G65W allele of human URAT1 leads to reduced urate transport in mammalian cells and therefore is causally related to lower serum urate levels and reduced gout risk.

Some limitations to our study warrant mention. The AA replication samples were of relatively small size, which—together with lower coverage even after imputation—limited statistical power for both the identification of novel loci as well as the replication of previously detected loci. Nevertheless, the magnitude of associations observed for serum urate was similar among AA for loci previously detected in EA populations. We relied on a single measurement of serum urate as well as on self-reported gout, which may have impacted our results to some degree. The fact that we were able to detect highly significant associations between SNPs at known urate- and gout-associated loci underscores the validity of the phenotype definitions.

In summary, our study supports the use of GWAS in populations of non-European ancestry for the discovery of novel trait-associated loci as well as additional risk variants at known loci. It further supports the use of experimental studies to confirm functionality of rare non-synonymous coding variants.

MATERIALS AND METHODS

Serum urate measurement, gout and covariates

Serum urate was measured as described in the Study-specific methods. Gout was defined using cohort-specific definitions based on self-report and medication intake as detailed in the Study-specific methods. Covariates used in analyses were age (years), sex as well as study center if applicable.

Genotyping platforms for genome-wide genotype and imputation

Genotyping in the CARe Consortium was conducted using two chips: the IBC SNP chip (32) in 7112 AA and 22 539 EA participants, and the Affymetrix 6.0 array in 6089 AA participants. Details about genotyping as well as imputation and data cleaning procedure are provided in Supplementary Material, Table S3. Data cleaning and SNP imputation for the individual cohorts were performed centrally by the CARe analytical group at the Broad institute. For imputation among AA participants, a combined HapMap 2 CEU + YRI reference panel was created, which includes SNPs segregating in both CEU and YRI, as well as SNPs segregating in one panel and monomorphic and non-missing in the other (2.74 million altogether). Imputation results were filtered at an RSQ_HAT threshold of 0.3 and a minor allele frequency threshold of 0.01. The imputation software was MACH 1.0.16 (33). Imputed SNPs were then analyzed as the SNP dosage, a continuous number between 0 and 2 corresponding to the estimated number of copies of the pre-specified allele. As the Affymetrix chip provides better coverage across the entire genome, whereas the IBC chip provides better coverage of selected regions including rare variants and was genotyped in more samples, data from the Affymetrix and IBC chip were analyzed separately.

Statistical methods for discovery stage 1

Phenotypes were ascertained as outlined above. Principal components were generated using EIGENSTRAT (34) with the curated CARe African-American Affymetrix 6.0 genotype data combined with 1178 European Americans (EA) (a multiple sclerosis GWAS graciously offered by Dr Phil de Jager and colleagues) and from 756 Nigerians from the Yoruba region (an hypertension GWAS graciously offered by Dr Richard Cooper and colleagues). The first principal component has a correlation >0.98 with global ancestry, which was generated using ANCESTRYMAP (35) and STRUCTURE (36).

Study-specific association analyses were performed centrally using linear regression for serum urate and logistic regression for gout, assuming an additive genetic model. For serum urate, we analyzed sex-specific residuals controlling for age and study center, when applicable. For gout, covariates were age, sex and study center, when applicable. All analyses were adjusted for 10 principal components; sensitivity analyses

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adjusting only for principal components that showed significant association with the outcome yielded similar results. When appropriate, the analyses accounted for relatedness using linear mixed-effect models for serum urate and logistic regression using generalized estimating equations for gout (37).

Meta-analyses of study-specific results were conducted separately for the Affymetrix 6.0 and the IBC chips using inverse-variance weighted fixed-effect models implemented in METAL (38). For the results from the Affymetrix 6.0 platform, genomic control correction was applied to individual-study results with genomic control factor (λ) >1 prior to meta-analysis. After meta-analysis, the lambda statistics were 1.02 (urate) and 0.99 (gout) for the GWAS indicating that there was no appreciable inflation of the test statistics. Genomic control corrections were not applied to the results from the IBC chip, which was not a genomic-wide array.

The statistical significance level was specified *a priori* at the conventional threshold of $\alpha = 5 \times 10^{-8}$ for the GWAS and as $\alpha = 2.0 \times 10^{-6}$ for the IBC chip analyses, which was based on an estimate of 25 000 independent SNPs with variance inflation factor <2 (39). Software used for data management, analysis and graphing included PLINK (40), Eigenstrat (34), METAL (38) and R (v2.9.0).

Stage 2 replication analysis

Six SNPs were selected for replication based on the following criteria: (i) the lead SNP in a locus met genome-wide significance and was not previously reported (rs9321453 in chromosome 6); (ii) the lead SNPs met genome-wide significance in a known locus and were in low LD ($r^2 < 0.2$) with the reported index SNP in EA individuals (rs606458, rs12800450 and rs493573 in chromosome 11); or (iii) SNPs met region-wide significance in the interrogation of known loci in the Affymetrix 6.0 array GWAS platform and were in low LD ($r^2 < 0.2$) with the reported index SNP in EA individuals (rs9679543 on chromosome 2 and rs589691 on chromosome 11).

Replication of these SNPs was attempted using genotyped and imputed *in silico* GWAS data from the replication cohorts. Serum urate was modeled as it was for the discovery cohorts, and an additive genetic model was used. The Study-specific methods provide more detail about the replication cohorts.

After return of the replication results, evidence for independent replication was assessed as one-sided nominal significance from the combined replication samples (1996 individuals, $P < 0.05$). Subsequently, a meta-analysis was conducted for the results from discovery and replication samples. Findings were considered replicated when the effect direction was consistent for the same modeled allele and the combined *P*-value from discovery and replication samples was both genome-wide significant and lower than the *P*-value from the discovery samples alone (41).

Statistical methods for locus interrogation

An interrogation of the 50 kb flanking regions around the known EA loci was conducted in our AA cohorts. In situations where the HapMap CEU haplotype block extended beyond the gene (*SLC22A11/12* and *GCKR* regions), the region of interrogation was extended up to a recombination hotspot or to 500 kb on both sides of the gene. Significance for this regional interrogation was set at $P < 0.05$ adjusted for the number of independent SNPs in the region as defined by pair-wise variance inflation factor < 2.

In regions in which multiple signals with low LD ($r^2 < 0.5$) were observed in association with serum urate, we conducted regression including multiple index SNPs in the loci as predictors using the ARIC AA sample, the largest sample among our AA cohorts, to assess the independence of the signals and the total contribution of these signals to serum urate variance.

Molecular biology

The use of human URAT1 in the expression vector pcDNA 3.1 was kindly permitted by H. Endou and has been described previously (24). The URAT1 mutation G65W was created using the QuikChange site-directed mutagenesis kit (Stratagene, Santa Clara, CA, USA) and the primers were 5′-CGG CTC AGG CCA GCA TCC TAT GGA GCT TGA GTC CTG AGG CCC-3′ and 5′-GGG CCT CAG GAC TCA AGC TCC ATA GGA TGC TGG CCT GAG CCG-3′. mRNA was prepared from the WT URAT1 and G65W URAT1 expression vectors using the MEGAscript kit (Ambion) according to the manufacturer's protocol.

Urate transport assays

For the urate transport assays, CHO cells were transiently transfected, using Lipofectamine 2000 (according to the manufacturer's protocol, Invitrogen, USA) with either URAT1, G65W URAT1 or blank vector. Because of the lack of a working commercial antibody, it was not possible to control for equal expression of the two constructs, but all experimental conditions except for the amino acid substitution were kept the same. Radio-labeled ^{14}C uric acid (American Radio-labeled Chemicals) was dissolved in a stock solution of 2 mM NaOH with a final uric acid concentration of 2 mM. After 24 h, the media were replaced with 100 μM ^{14}C urate containing minimal Ham's F12 media with L-glutamine. Cells were incubated for 1 h at 37°C, then washed twice with ice-cold Ham's F-12 media and once with phosphate buffered saline. 1 N NaOH was added to lyse the cells, and the cells and contents scraped, added to a scintillation tube and measured using a Beckman Scintillation counter. Results from each day were normalized to the highest count recorded to allow for cross day comparisons. For each batch of counting, a set of control vials of known volume and concentration of ^{14}C uric acid was included, allowing for a calculation of ^{14}C uric acid concentrations based on the counts measured in any of the experimental samples. URAT1 (or URAT1 G65W) specific transport activity was calculated by subtracting the transport activity measured in the control cells transfected with the blank vector from the one measured in URAT1-expressing cells. Significance was evaluated using a two-tailed Student's *t*-test.

Study-specific methods

ARIC. The ARIC study is a population-based, prospective study in four US communities. From 1987 to 1989, 15 792

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mostly white and AA participants aged 45–64 years were recruited by probability sampling and underwent a baseline examination (visit 1), and were examined three more times, roughly every 3 years (42). For this study, participants were excluded for non-consent to genetic research, or if they did not self-identify as black or white. Institutional Review Boards of the participating institutions (Johns Hopkins University, University of Minnesota, Wake Forest University, University of Mississippi, Baylor University, University of Texas and University of North Carolina) approved the study protocols. All participants provided written informed consent.

In the ARIC study, uric acid concentration was measured with the uricase method at visit 1 (43). Gout status was obtained by self-report at visit 4. Age and sex were obtained by self-report at baseline.

CARDIA. Study design details of Coronary Artery Risk Development In Young Adults (CARDIA) have been previously published (44). Briefly, CARDIA recruited a cohort of young black and white adults, age 18–30 at the time of enrollment. From 1985 to 1986, CARDIA recruited participants from four sites: Birmingham, AL, USA; Chicago, IL, USA; Minneapolis, MN, USA; and Oakland, CA, USA. Follow-up examinations occurred at years 2, 5, 7, 10, 15 and 20. Serum urate was from baseline and measured by the uricase method. Gout status was collected at years 7, 10 and 15 by self-report.

CHS. The Cardiovascular Health Study (CHS) is a community-based longitudinal study of risk factors for cardiovascular disease and stroke in adults 65 years of age or older, recruited at four field centers (Forsyth County, NC, USA; Sacramento County, CA, USA; Washington County, MD, USA; and Pittsburgh, PA, USA) (45). A total of 5201 predominantly Caucasian individuals were recruited in 1989–1990 from random samples of Medicare eligibility lists, followed by an additional 687 African-Americans recruited in 1992–1993 (total $n = 5888$). Baseline serum urate was measured on the Kodak Ektachem 700 Analyzer.

FHS. The Framingham Heart Study began in 1948 when the Original Cohort was enrolled (46). Beginning in 1971, the Offspring Cohort was enrolled (5124 participants); the methodology and design has been described (47–48). In 2002, the Third Generation cohort was enrolled ($n = 4095$) (49). Participants for the current study include individuals from the offspring cohort and the Third Generation who attended the first examination. Serum urate was measured at the first examination cycle in every cohort with an autoanalyzer with a phosphotungstic acid reagent (50). Gout was self-reported in the offspring cohort during examination cycles 3 to 7, and in the third-generation group during first examination.

JHS. The Jackson Heart Study is a single-site, longitudinal, population-based study. The sample consists of 5302 African-American women and men selected between 2000 and 2004 (first visit) from the tricounty area encompassing Jackson, MS (51). DNA and consent for data sharing consistent with NIH guidelines were available for 3443 participants for the CARe Consortium. Baseline serum urate was measured using the uricase method.

HANDLS. The Healthy Aging in Neighborhoods of Diversity Across the Life Span study is a prospective longitudinal, multidisciplinary study. Subjects were recruited as a fixed cohort of participants by household screenings from an area probability sample of 12 census segments in the city of Baltimore, MD, USA. These tracts were selected to yield representative distributions of AA and whites, men and women, and individuals with SES $<125\%$ federal poverty level and $\geq 125\%$ federal poverty level. Study design and participant characteristics were previously reported (52). Uric acid was measured in serum from fasting blood samples by spectrophotometry at Quest Diagnostics Laboratories in Chantilly, Virginia.

HUFS. The Howard University Family Study is a population-based study of AA families enrolled from the Washington, D.C. metropolitan area (53). In the first phase of recruitment, a randomly ascertained sample of 350 AA families with members in multiple generations from the Washington, D.C. metropolitan area were enrolled and examined. Families were not ascertained based on any phenotype. In a second phase of recruitment, additional unrelated individuals from the same geographic area were enrolled to facilitate nested case–control study designs. The total number of recruited individuals was 2028, of which 1976 remained after data cleaning. From this sample, 1007 unrelated individuals were included for the serum urate analysis. Serum urate was measured using the COBAS Integra Uric Acid ver.2 assay from Roche Diagnostics (Indianapolis, IN, USA).

SUPPLEMENTARY MATERIAL

Supplementary Material is available at *HMG* online.

ACKNOWLEDGMENTS

The authors wish to acknowledge the support of the National Heart, Lung and Blood Institute and the contributions of the research institutions, study investigators, field staff and study participants in creating this resource for biomedical research. We would like to thank Dr Yohannes Hagos who kindly provided the URAT1 plasmid, Dr H. Endou for the permission to use it, as well as Dr William B. Guggino for contributing experimental resources.

Conflict of Interest statement. None declared.

FUNDING

The following nine studies have contributed parent study data, ancillary study data and DNA samples through the Massachusetts Institute of Technology, Broad Institute (N01-HC-65226) to create this genotype/phenotype data base for wide dissemination to the biomedical research community:

Atherosclerosis Risk in Communities (ARIC): University of North Carolina at Chapel Hill (N01-HC-55015), Baylor Medical College (N01-HC-55016), University of Mississippi Medical Center (N01-HC-55021), University of Minnesota (N01-HC-55019), Johns Hopkins University (N01-HC-55020), University of Texas, Houston (N01-HC-55022), University of North Carolina, Forsyth County (N01-HC-55018);

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Cardiovascular Health Study (CHS): University of Washington (N01-HC-85079), Wake Forest University (N01-HC-85080), Johns Hopkins University (N01-HC-85081), University of Pittsburgh (N01-HC-85082), University of California, Davis (N01-HC-85083), University of California, Irvine (N01-HC-85084), New England Medical Center (N01-HC-85085), University of Vermont (N01-HC-85086), Georgetown University (N01-HC-35129), Johns Hopkins University (N01 HC-15103), University of Wisconsin (N01-HC-75150), Geisinger Clinic (N01-HC-45133), University of Washington (N01 HC-55222, U01 HL080295); Cleveland Family Study (CFS): Case Western Reserve University (NIH HL 46380, M01RR00080); Cooperative Study of Sickle Cell Disease (CSSCD): University of Illinois (N01-HB-72982, N01-HB-97062), Howard University (N01-HB-72991, N01-HB-97061), University of Miami (N01-HB-72992, N01-HB-97064), Duke University (N01-HB-72993), George Washington University (N01-HB-72994), University of Tennessee (N01-HB-72995, N01-HB-97070), Yale University (N01-HB-72996, N01-HB-97072), Children's Hospital-Philadelphia (N01-HB-72997, N01-HB-97056), University of Chicago (N01-HB-72998, N01-HB-97053), Medical College of Georgia (N01-HB-73000, N01-HB-97060), Washington University (N01-HB-73001, N01-HB-97071), Jewish Hospital and Medical Center of Brooklyn (N01-HB-73002), Trustees of Health and Hospitals of the City of Boston, Inc. (N01-HB-73003), Children's Hospital-Oakland (N01-HB-73004, N01-HB-97054), University of Mississippi (N01-HB-73005), St Luke's Hospital-New York (N01-HB-73006), Alta Bates-Herrick Hospital (N01-HB-97051), Columbia University (N01-HB-97058), St Jude's Children's Research Hospital (N01-HB-97066), Research Foundation, State University of New York-Albany (N01-HB-97068, N01-HB-97069), New England Research Institute (N01-HB-97073), Interfaith Medical Center-Brooklyn (N01-HB-97085); Coronary Artery Risk in Young Adults (CARDIA): University of Alabama at Birmingham (N01-HC-48047), University of Minnesota (N01-HC-48048), Northwestern University (N01-HC-48049), Kaiser Foundation Research Institute (N01-HC-48050), University of Alabama at Birmingham (N01-HC-95095), Tufts-New England Medical Center (N01-HC-45204), Wake Forest University (N01-HC-45205), Harbor-UCLA Research and Education Institute (N01-HC-05187), University of California, Irvine (N01-HC-45134, N01-HC-95100); Framingham Heart Study (FHS): Boston University (N01-HC-25195, R01HL092577-01A1, RO1 HL076784, R01 AG028321); Jackson Heart Study (JHS): Jackson State University (N01-HC-95170), University of Mississippi (N01-HC-95171), Tougaloo College (N01-HC-95172); Multi-Ethnic Study of Atherosclerosis (MESA): University of Washington (N01-HC-95159), Regents of the University of California (N01-HC-95160), Columbia University (N01-HC-95161), Johns Hopkins University (N01-HC-95162, N01-HC-95168), University of Minnesota (N01-HC-95163), Northwestern University (N01-HC-95164), Wake Forest University (N01-HC-95165), University of Vermont (N01-HC-95166), New England Medical Center (N01-HC-95167), Harbor-UCLA Research and Education Institute (N01-HC-95169), Cedars-Sinai Medical Center (R01-HL-071205), University of Virginia (subcontract to R01-HL-071205); and Sleep Heart Health Study (SHHS): Johns Hopkins University (U01 HL064360), Case Western University (U01 HL063463), University of California, Davis (U01 HL053916), University of Arizona (U01 HL053938), University of Minnesota (relocating in 2006 to Univ Arizona) (U01 HL053934), University of Pittsburgh (U01 HL077813), Boston University (U01 HL053941), MedStar Research Institute (U01 HL063429) and Johns Hopkins University (U01 HL053937).

Healthy Aging in Neighborhoods of Diversity across the Life Span Study (HANDLS): this research was supported by the Intramural Research Program of the NIH, National Institute on Aging and the National Center on Minority Health and Health Disparities (intramural project # Z01-AG000513 and human subjects protocol # 2009-149). Data analyses for the HANDLS study utilized the high-performance computational capabilities of the Biowulf Linux cluster at the National Institutes of Health, Bethesda, Md. (http://biowulf.nih.gov).

Howard University Family Study (HUFS): The Howard University Family Study was supported by National Institutes of Health grants S06GM008016-320107 and S06GM008016-380111. Enrollment was carried out at the Howard University General Clinical Research Center, supported by National Institutes of Health grant 2M01RR010284. This research was supported in part by the Intramural Research Program of the Center for Research on Genomics and Global Health. The Center for Research on Genomics and Global Health is supported by the National Human Genome Research Institute, the National Institute of Diabetes and Digestive and Kidney Diseases, the Center for Information Technology and the Office of the Director at the National Institutes of Health (Z01HG200362). Genotyping support was provided by the Coriell Institute for Medical Research. We thank the participants of the Howard University Family Study. The contents of this publication are solely the responsibility of the authors and do not necessarily represent the official view of the National Institutes of Health.

Individual support: O.M.W. was supported by NIDDK: DK032753-25A1, A.K. was supported by the Emmy Noether Programme of the German Research Foundation.

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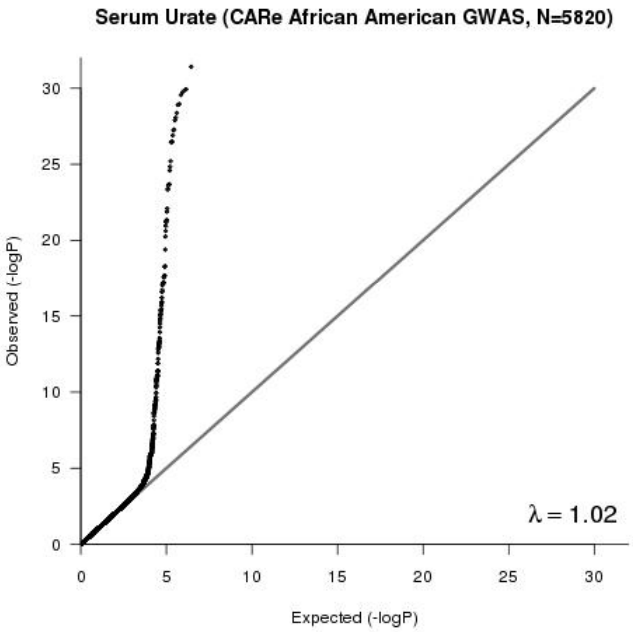
Genome-wide Association Study for Serum Urate Concentrations and Gout among African Americans Identifies Genomic Risk Loci and a Novel URAT1 Loss-of-Function Allele

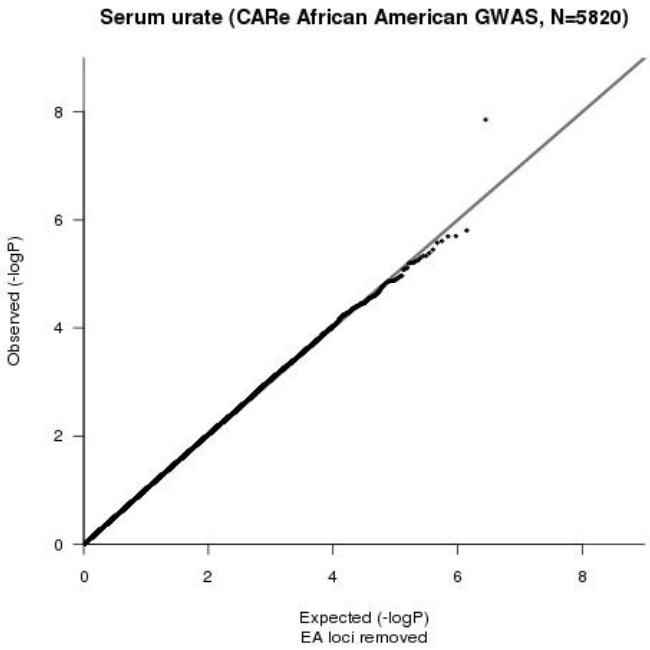
Supplementary Figures

Supplementary figure 1A, B, C. QQ Plots of GWAS results among African Americans with serum urate for all SNPs (A), with known loci removed (B), with gout (C).

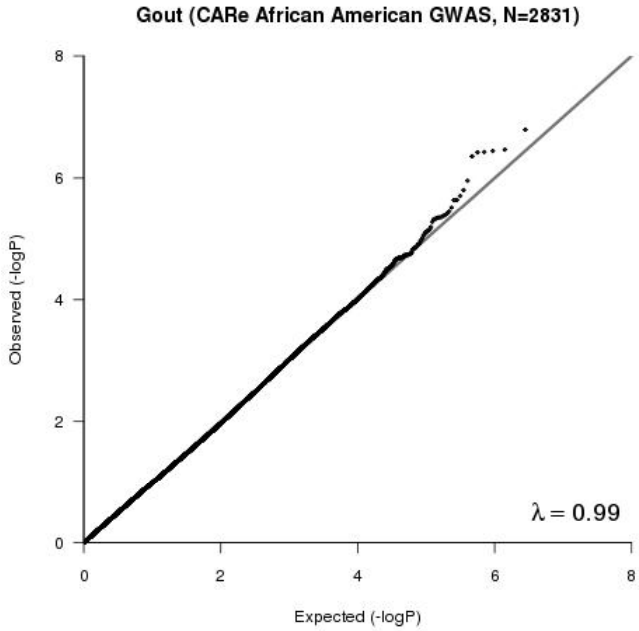
Supplementary Figure 1A



Supplementary Figure 1B



Supplementary Figure 1C



Supplementary figure 2A, B, C. Panel A shows CHARGE serum urate GWAS results in the SGK1 region. The position where the CARe African American GWAS detected genome-wide significant signal is highlighted with a blue arrow. Panel B and C show the haplotype blocks determined by r^2 in HapMap release 22 CEU and YRI populations respectively.

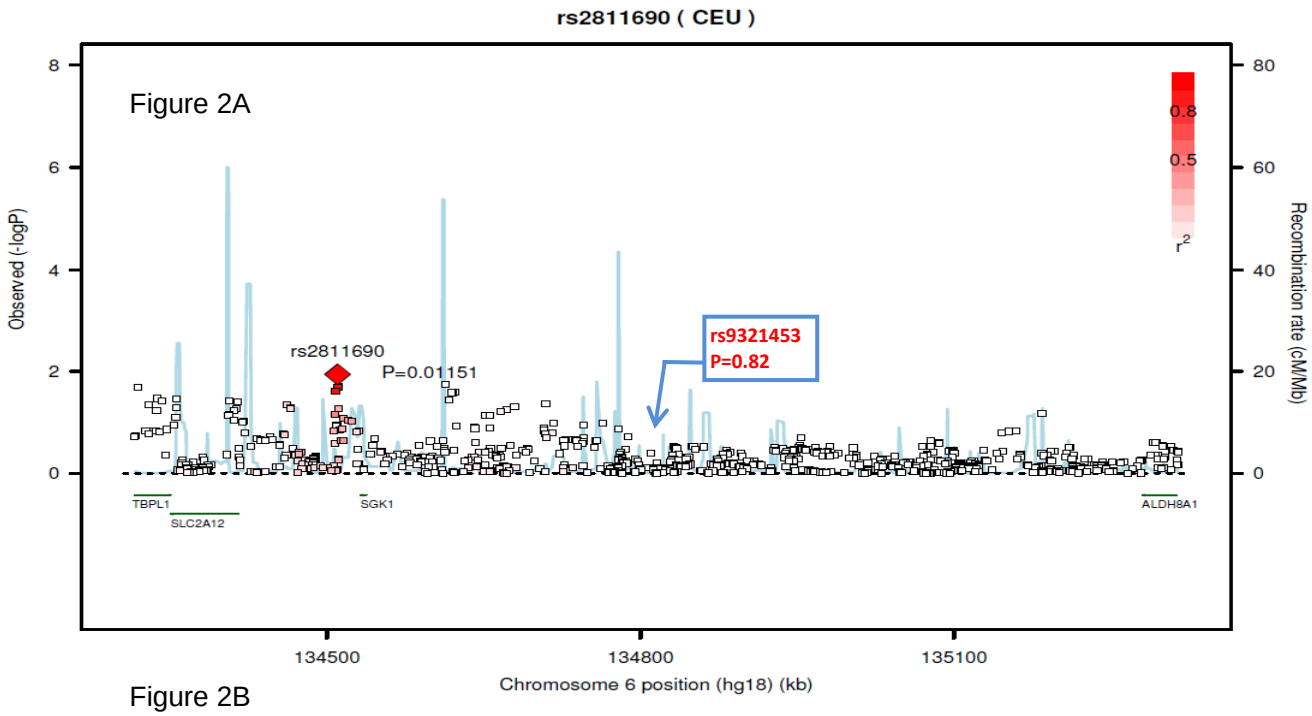


Figure 2B

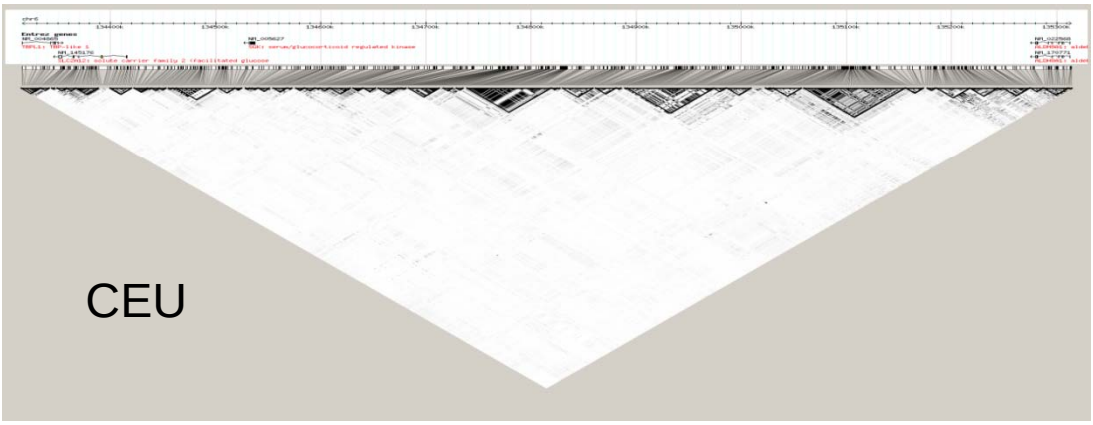
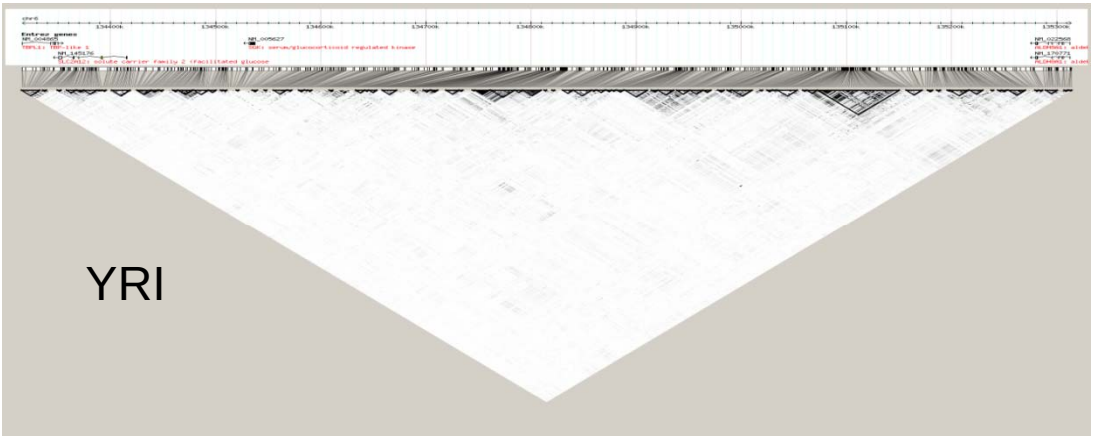
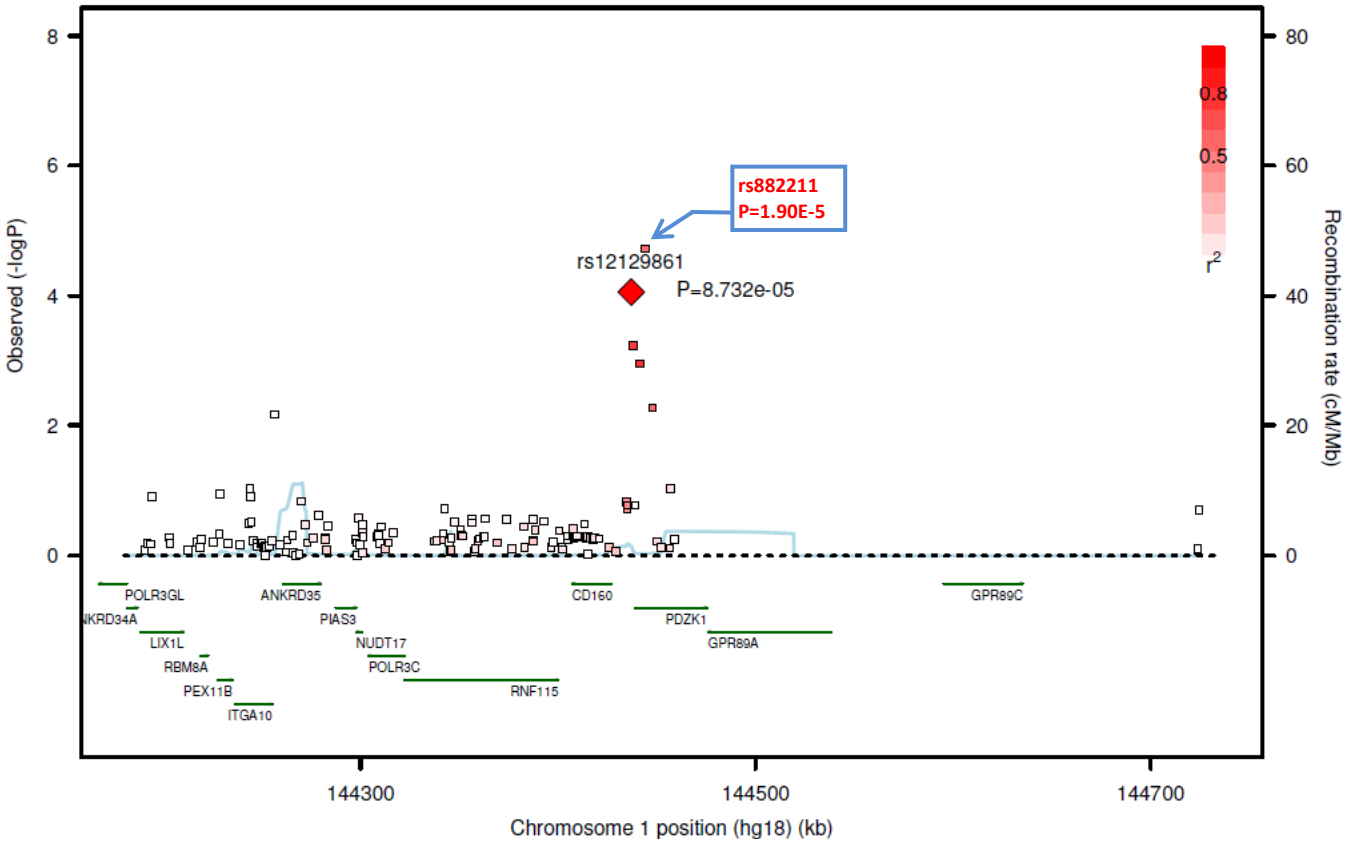


Figure 2C

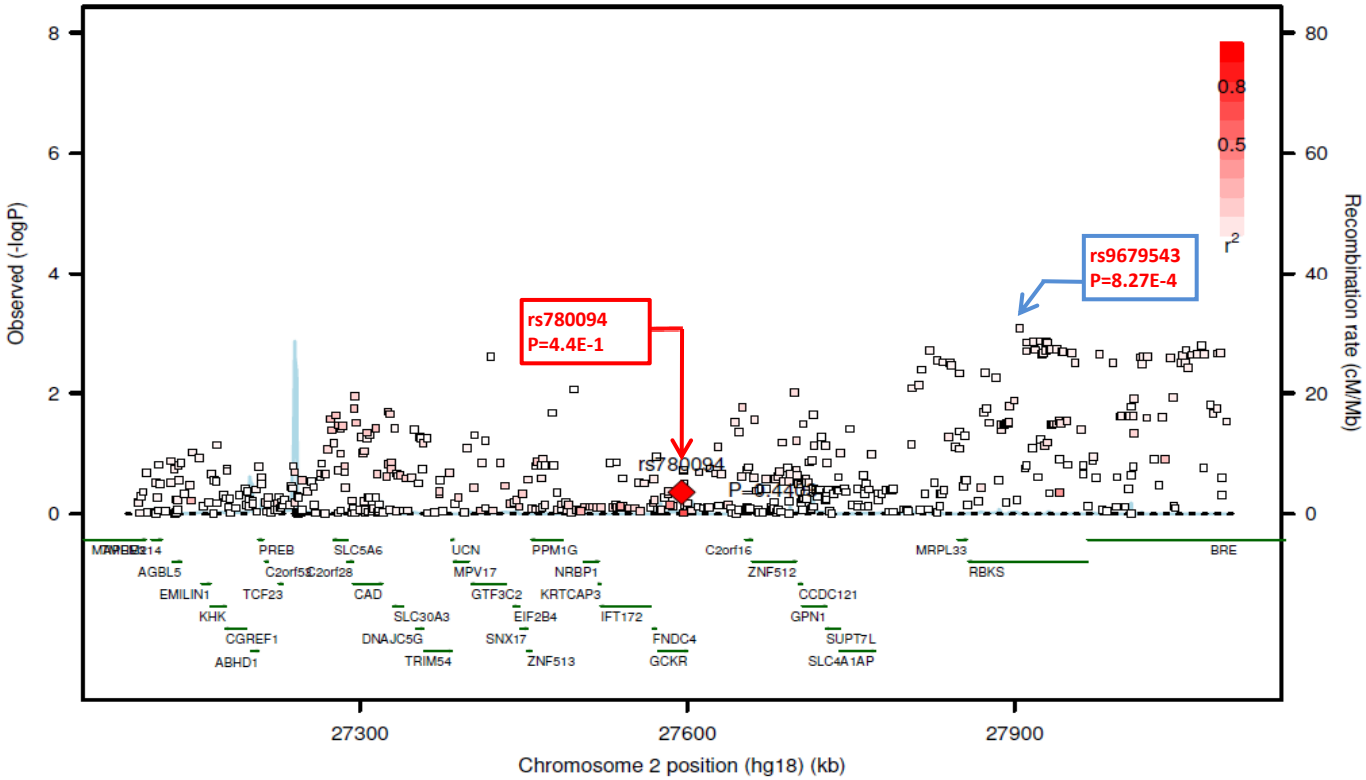


Supplementary Figure 3A – 3K. Regional Association Plot of AA serum urate GWAS results for loci reported in studies of EA individuals. The index SNP in EA individuals are represented by a red diamond. Best SNPs in AA are pointed to by blue arrows.

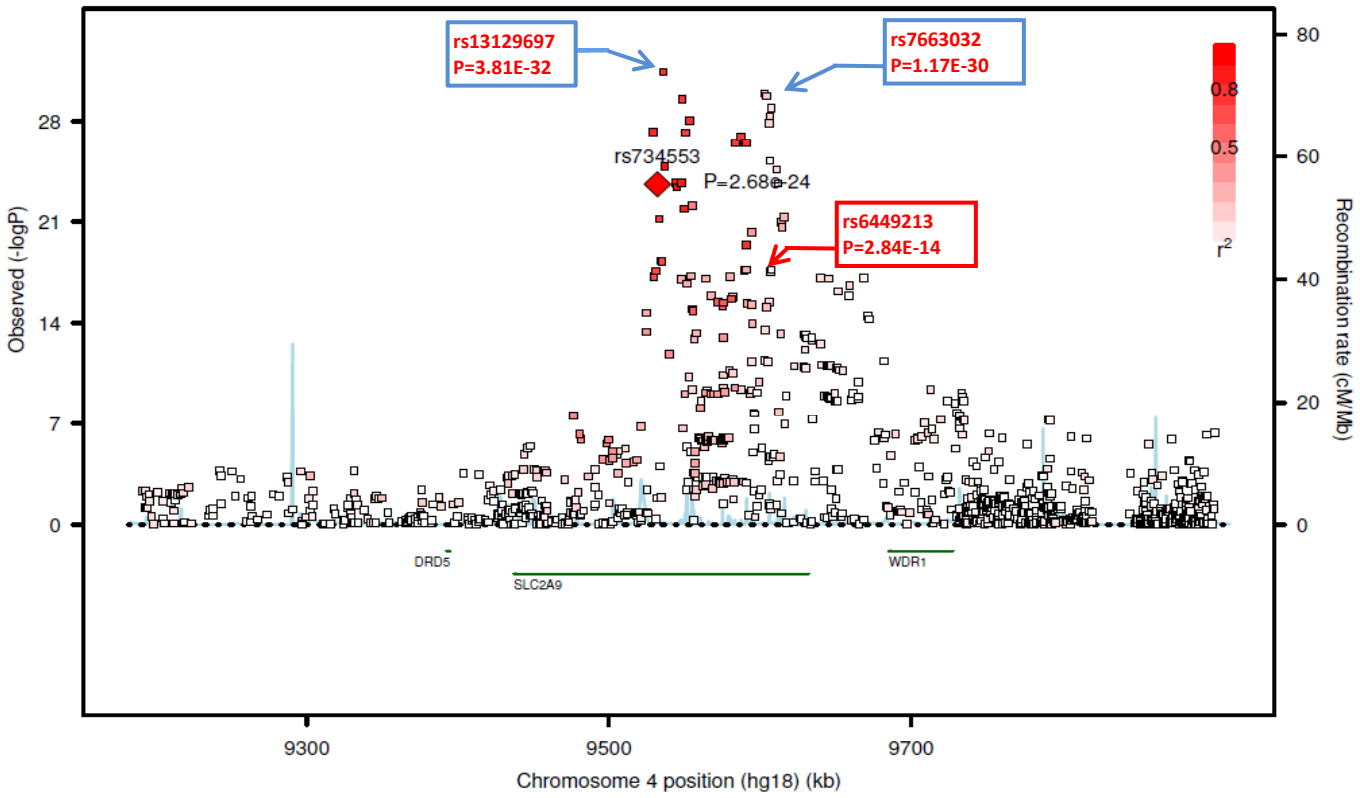
Supplementary Figure 3A PDZK1



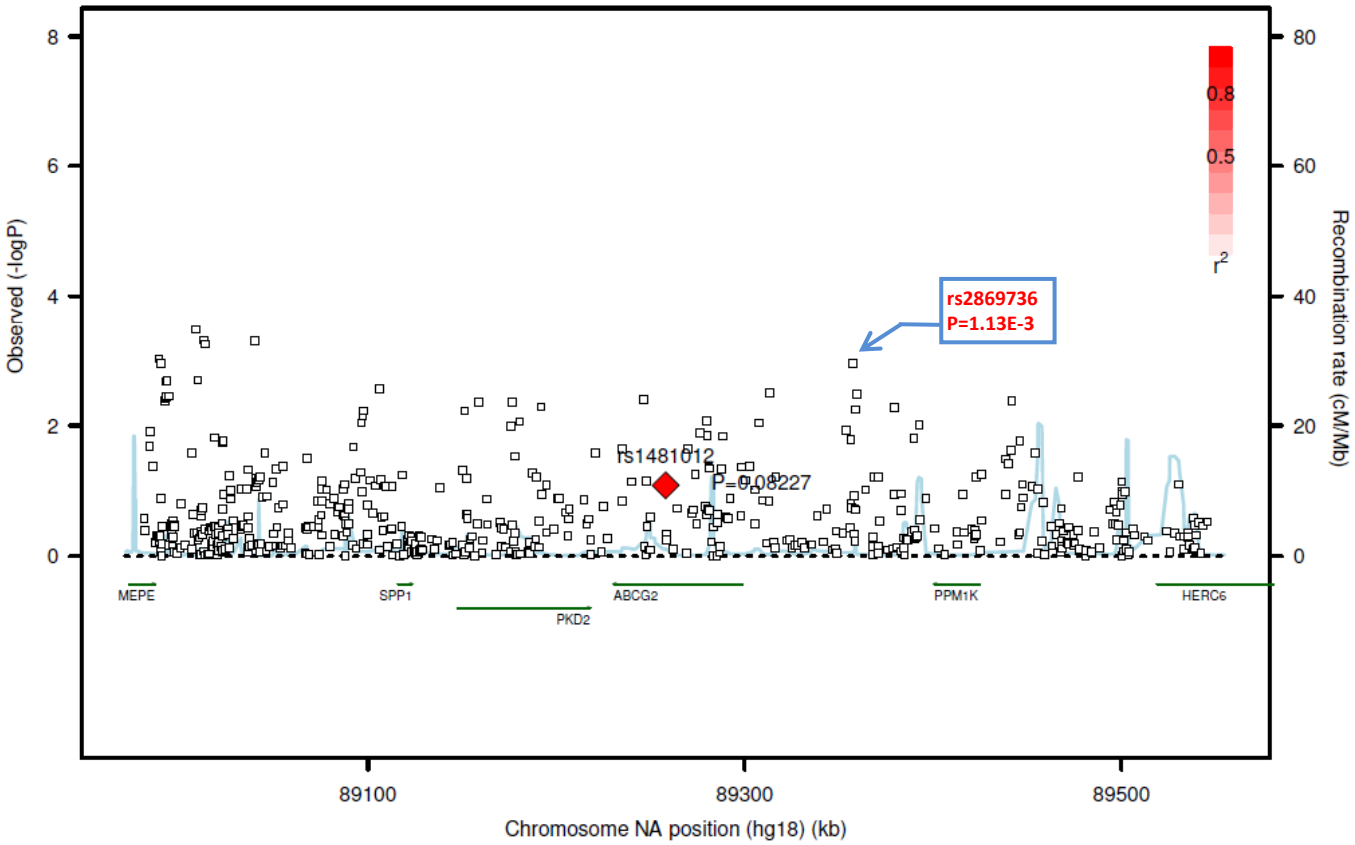
Supplementary Figure 3B GCKR



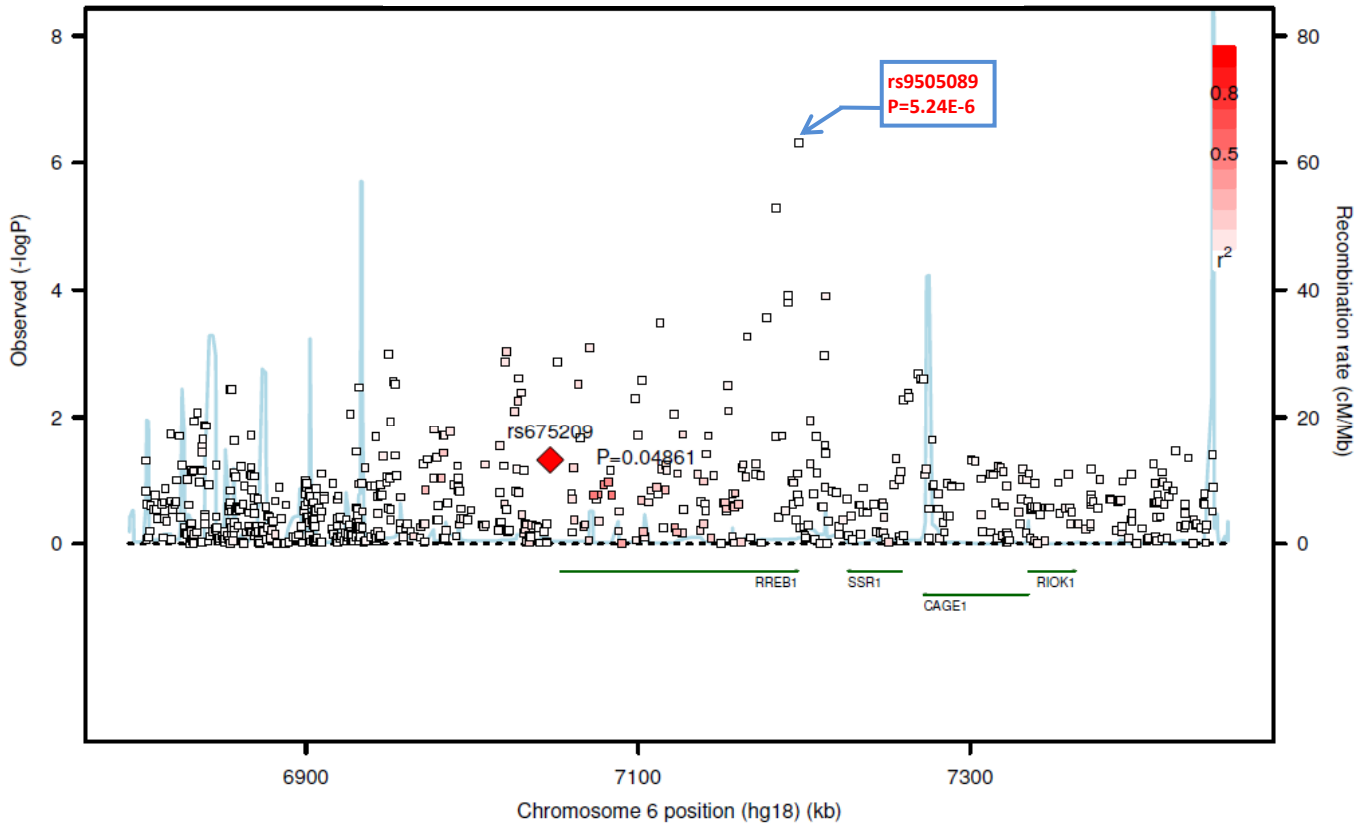
Supplementary Figure 3C SLC2A9



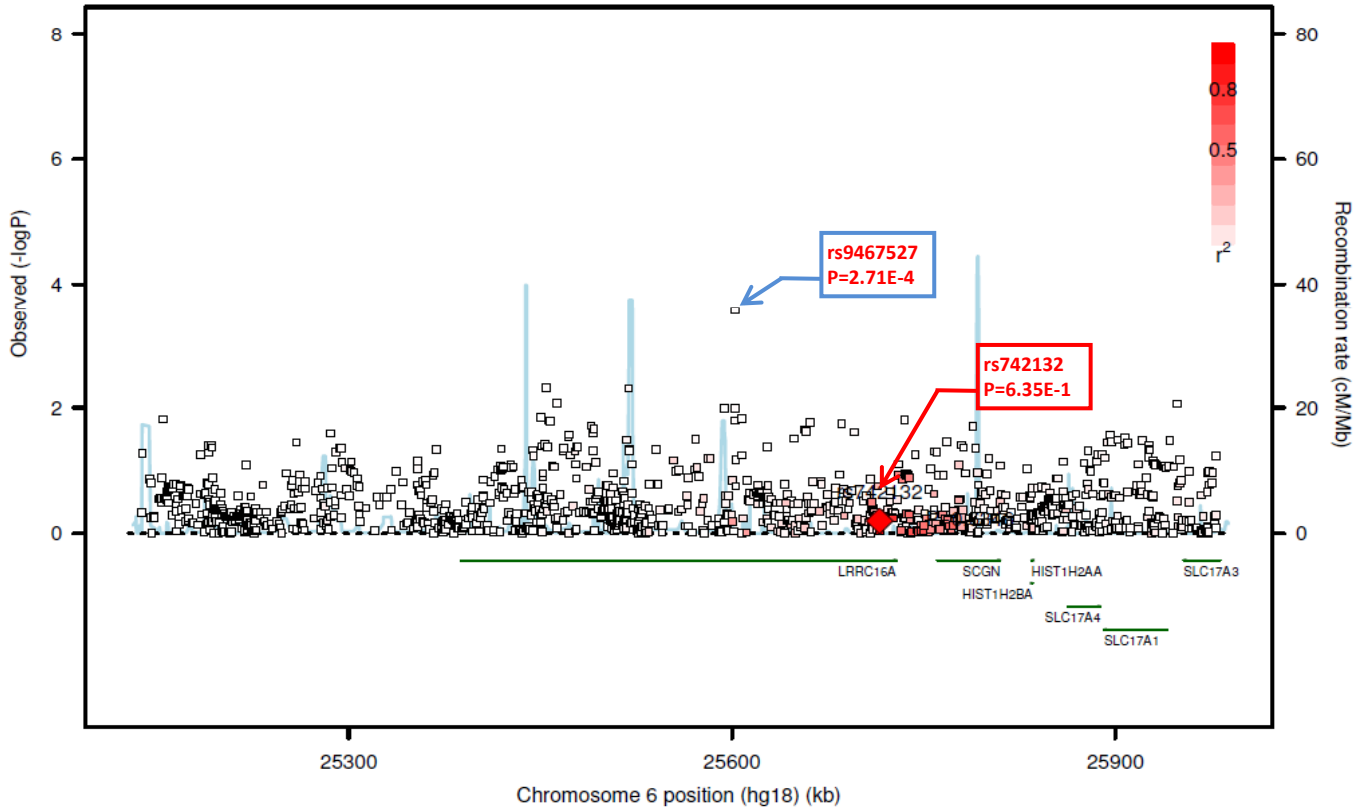
Supplementary Figure 3D ABCG2



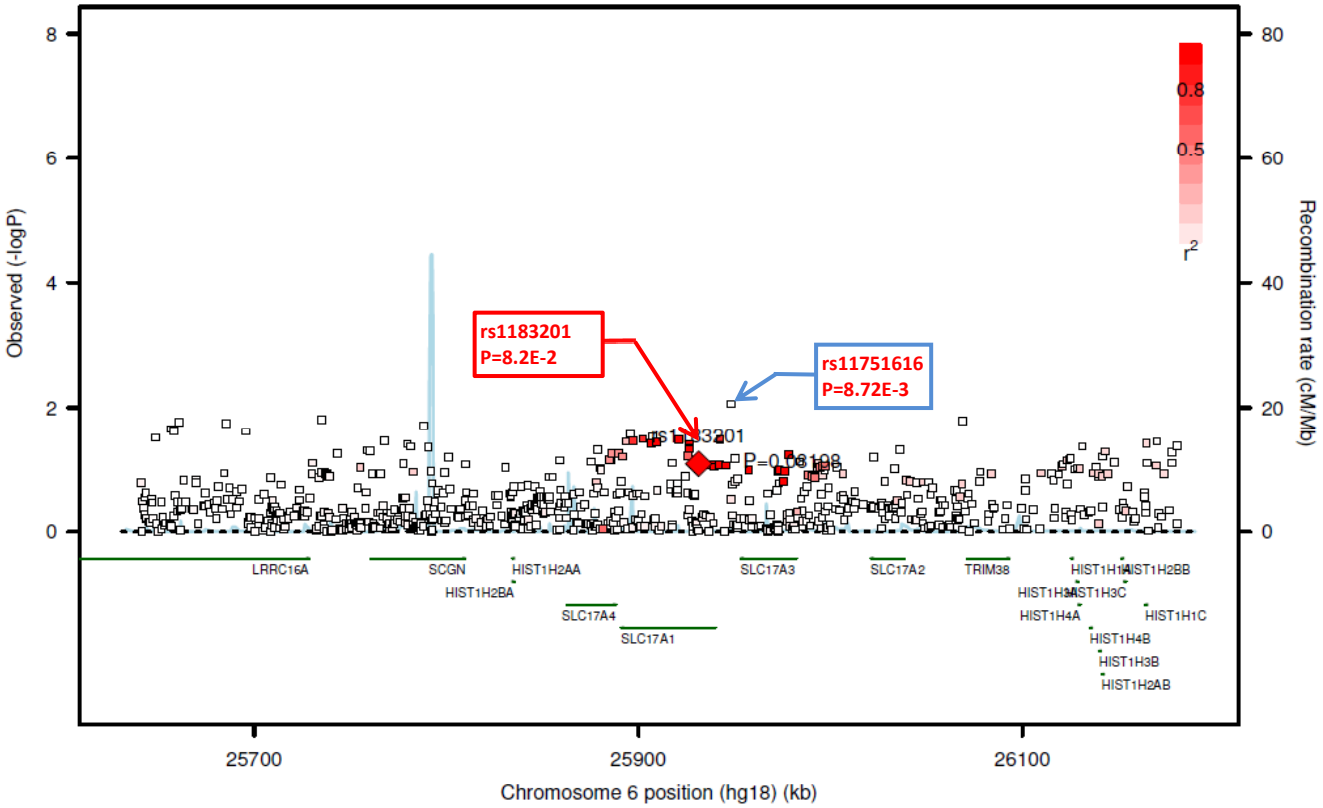
Supplementary Figure 3E RREB1



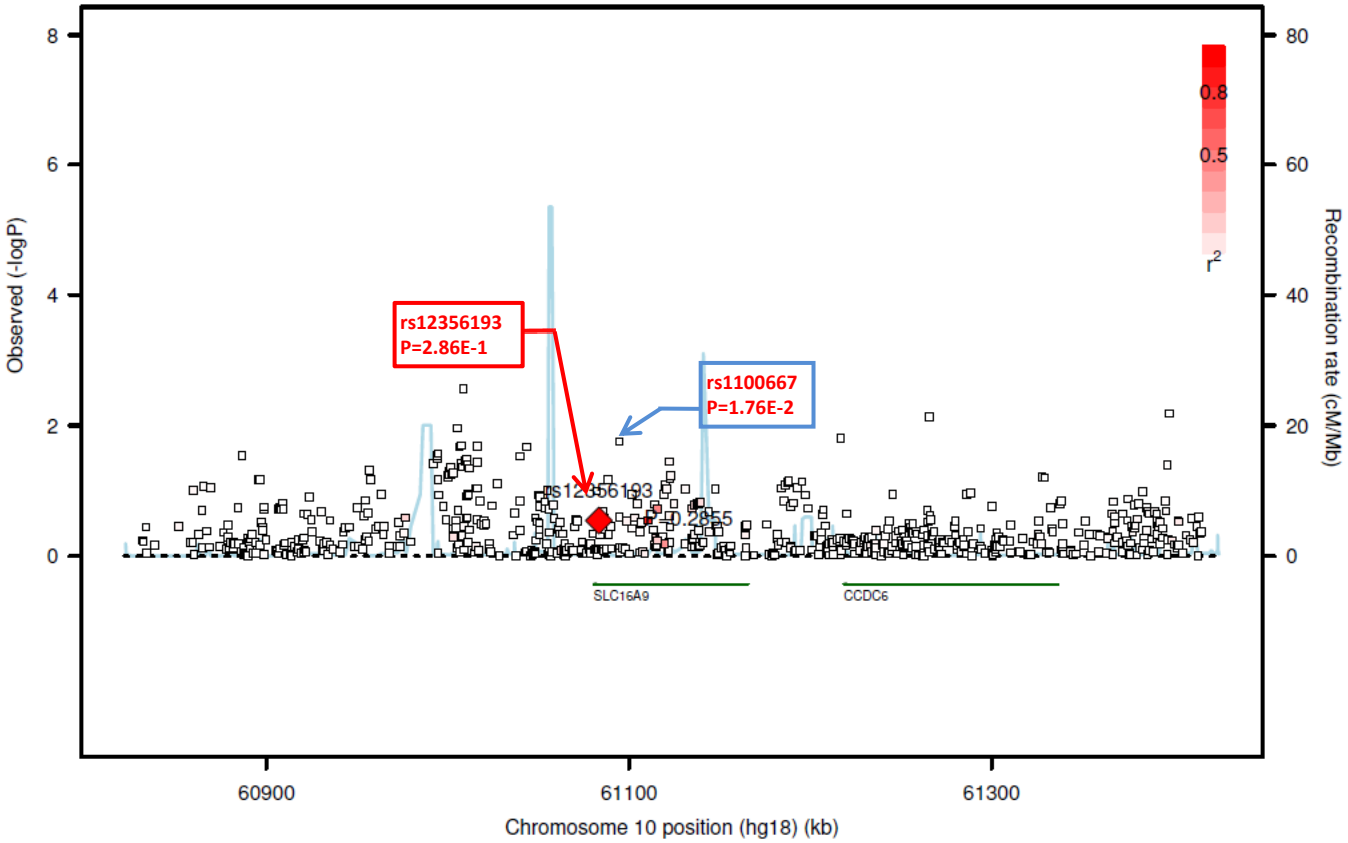
Supplementary Figure 3F LRRC16



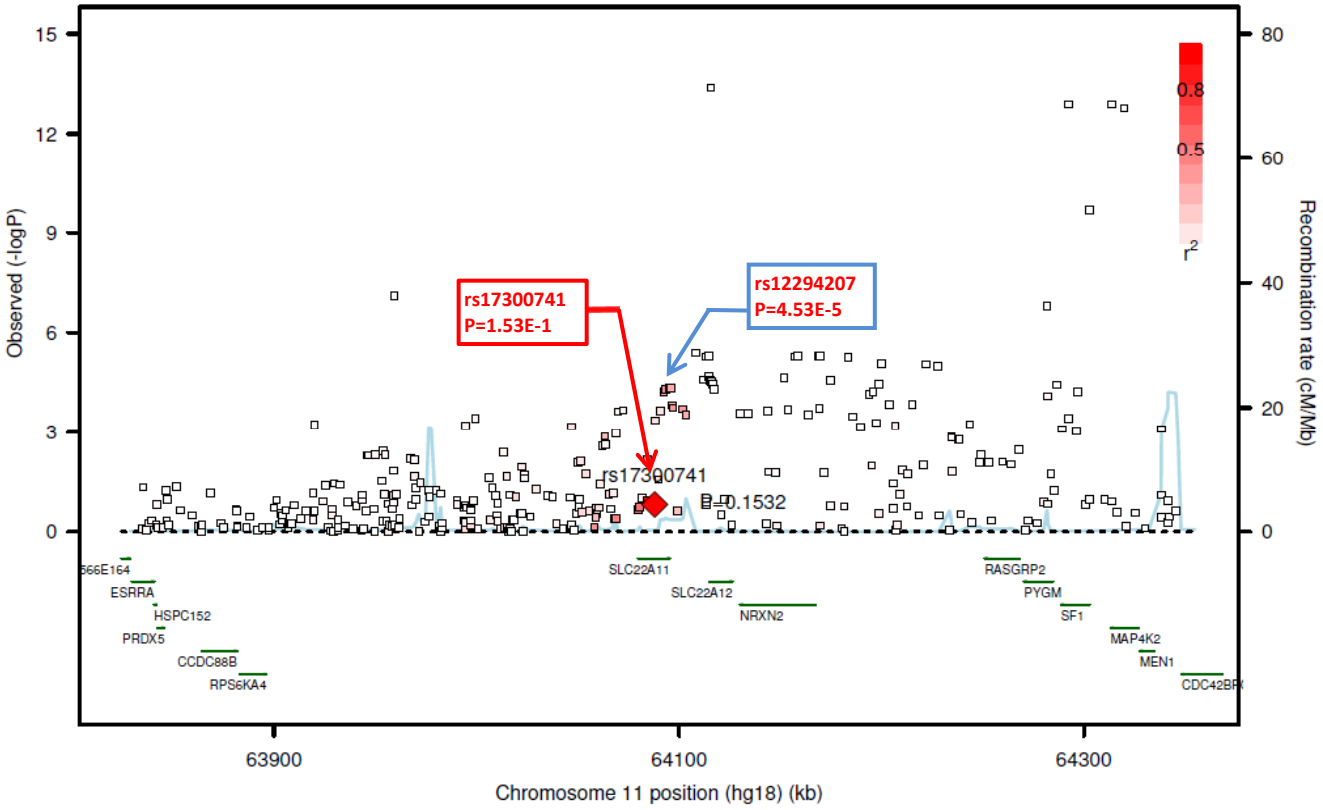
Supplementary Figure 3G SLC17A1



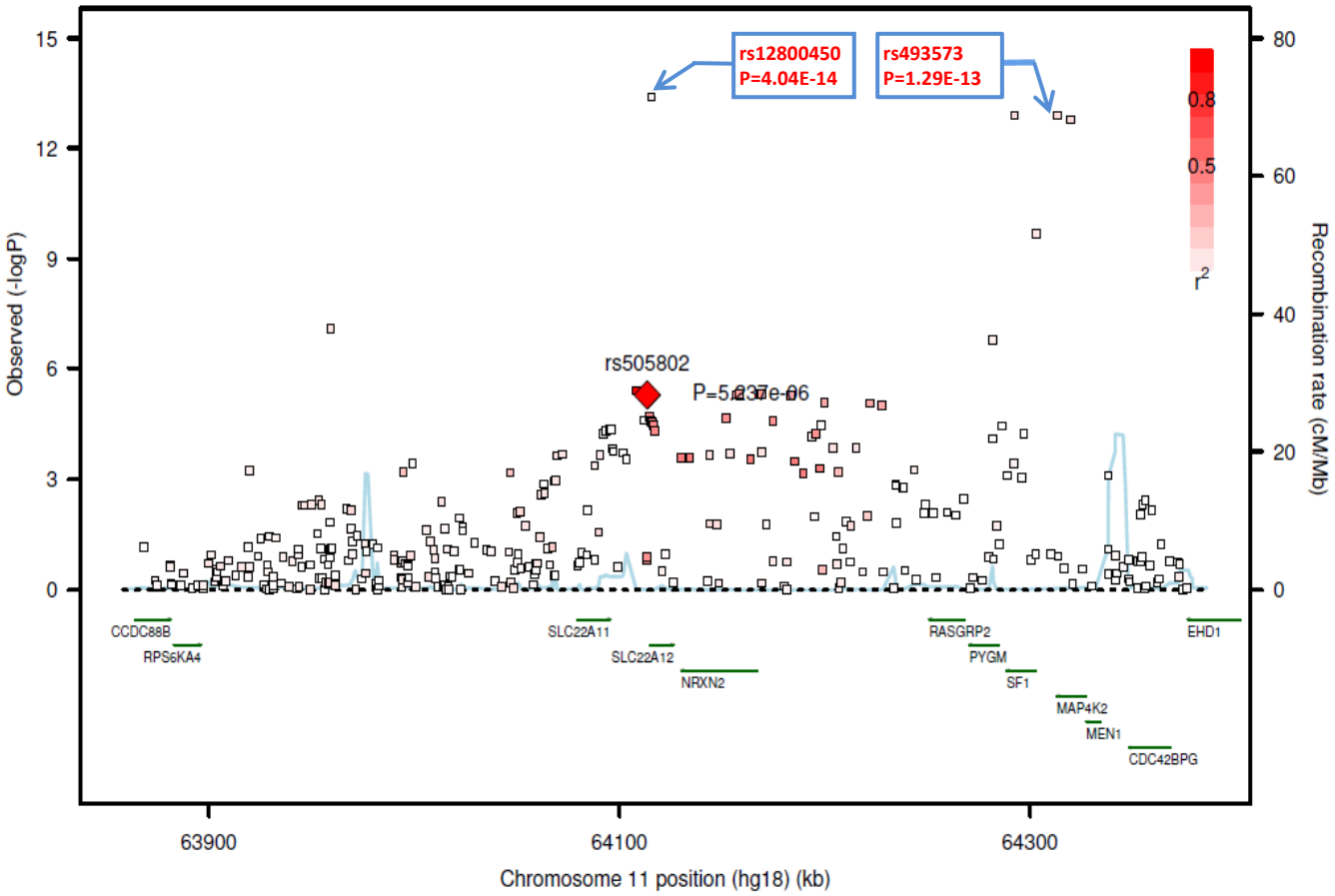
Supplementary Figure 3H SLC16A9



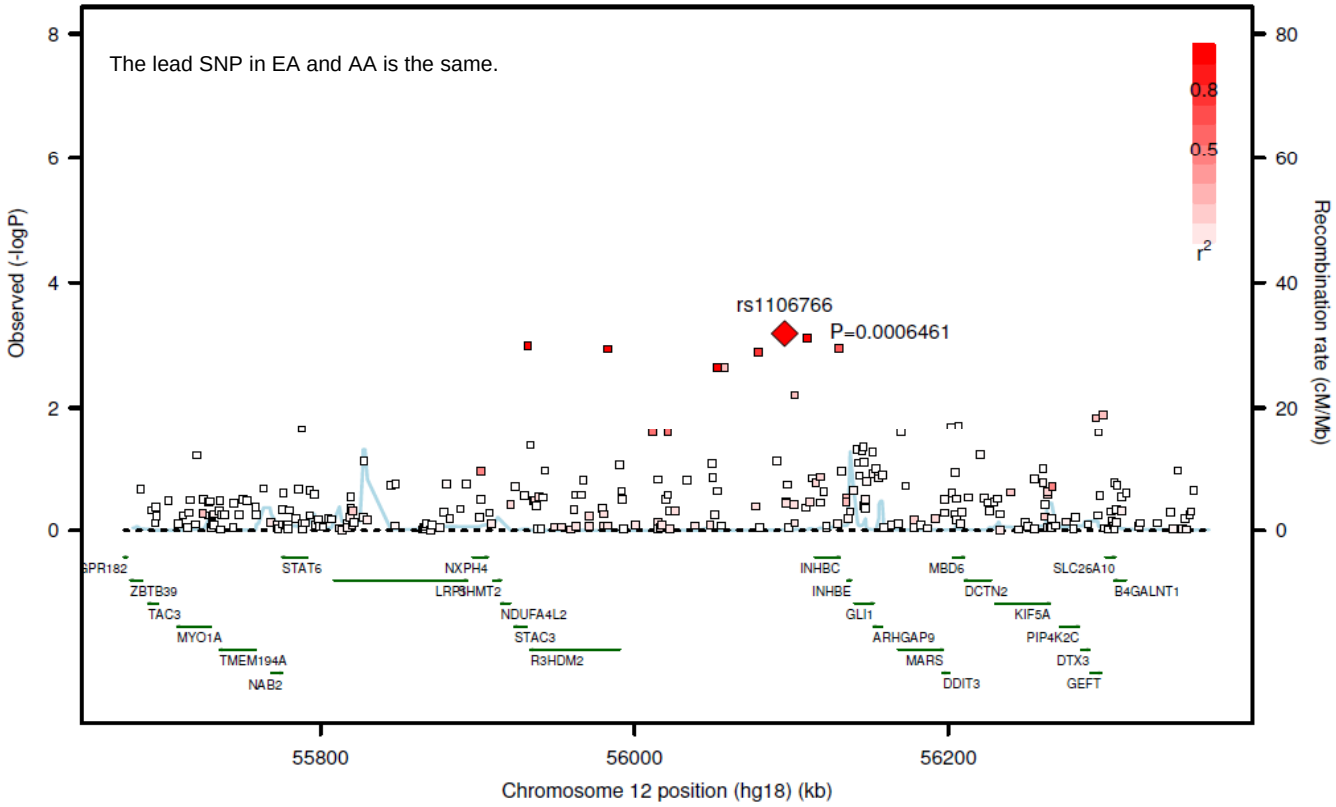
Supplementary Figure 3I SLC22A11



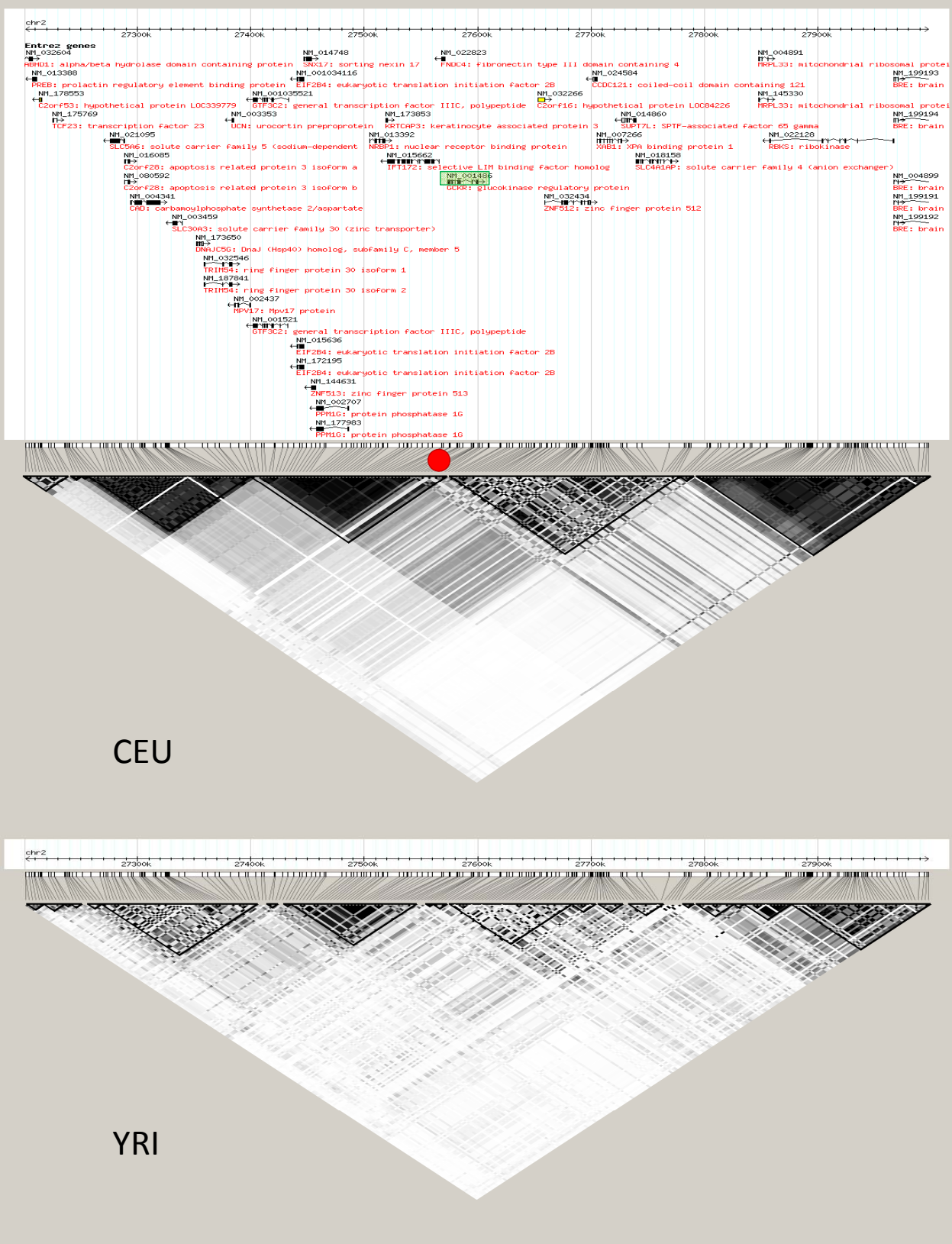
Supplementary Figure 3J SLC22A12



Supplementary Figure 3K R3HDM2



Supplementary Figure 4. GCKR region (Chr 2, 27200kb to 28000kb) r^2 of CEU and YRI from HapMap release 22. The red dot marks the approximate positions of rs780094, the index SNP in EA. The GCKR gene is highlighted in green. Supplementary Figure 3B shows the regional association of serum urate in CARe AA sample.



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

Supplementary Tables

Supplementary Table 1 - Replication and Meta-analysis Results

		HUFS					HANDLS					Replication		Meta-analysis	
SNP ID	A1	N	AF	Beta	SE	*P*-value	N	AF	Beta	SE	*P*-value	Beta	*P*-value	Beta	*P*-value
rs9321453	T	1007	0.43	0.16	0.07	1.9×10^{-02}	989	0.42	0.06	0.07	4.2×10^{-01}	0.11	2.4×10^{-02}	0.14	1.01×10^{-09}
rs9679543	T	1007	0.54	0.00	0.07	9.5×10^{-01}	989	0.53	-0.03	0.07	7.1×10^{-01}	-0.01	7.6×10^{-01}	0.07	4.79×10^{-03}
rs12800450	T	NA	NA	NA	NA	NA	989	0.01	-1.08	0.38	5.0×10^{-03}	-1.08	5.0×10^{-03}	-1.19	2.66×10^{-16}
rs589691	T	1007	0.33	-0.05	0.08	5.5×10^{-01}	989	0.31	-0.11	0.08	1.4×10^{-01}	-0.08	1.3×10^{-01}	-0.15	9.06×10^{-08}
rs606458	T	1007	0.37	-0.12	0.08	1.1×10^{-01}	989	0.37	-0.10	0.07	1.9×10^{-01}	-0.11	3.9×10^{-02}	-0.18	5.51×10^{-11}
rs493573	T	1007	0.02	-0.86	0.30	4.5×10^{-03}	989	0.02	-0.67	0.24	4.7×10^{-03}	-0.74	6.9×10^{-05}	-0.80	1.86×10^{-17}

A1: coded allele, AF: coded allele frequency. HUFS: Howard University Family Study, HANDLS: Healthy Aging in Neighborhoods of Diversity across the Life Span Study.

Supplementary Table 2. Association with Serum Urate among Participants of European Ancestry from the CHARGE consortium for the Results of the Genome-Wide Significant SNPs in CARe African Americans in Table 2

SNP	Chr	Genes within 60 kb	Position (b36)	CHARGE Coded Allele	CHARGE beta in mg/dl	CHARGE p-value	CHARGE MAF	HapMap Rel 22 MAF
rs9321453	6	NA	134815247	T	-0.003	8.18E-01	0.30	0.30
rs13129697	4	*SLC2A9*	9536065	T	0.37	1.46E-242	0.27	0.35
rs7663032	4	*SLC2A9*	9602936	T	0.37	6.34E-160	0.24	0.308
rs606458	11	MEN1;SF1;MAP4K2	64302967	T	-0.07	7.99E-06	0.10	0.092

Results for rs12800450 and rs493573 were not obtained because they were not present in any (rs493573) or only in a subset of CHARGE cohorts (rs12800450) with frequencies as low as 0.01%, making the estimates not reliable.

Supplementary Table 3 – Significant (*p*-value < 2.0×10^{-6}) Loci in European-ancestry individuals from the IBC Chip: SNP Association with Serum Urate and Gout

Trait	SNP ID	Chr	position (b36)	Genes Within 60 kb	SNP function	Coded Allele Frequency	Coded Allele	Beta	Trait Discovery *P*-value
Urate	rs1260326	2	27584444	*GCKR*	non-synonymous coding	0.42	T	0.09	7.7×10^{-14}
Urate	rs2241480	4	9684583	*WDR1*, *SLC2A9*	Intronic	0.30	T	0.22	2.3×10^{-29}
Urate	rs2231142	4	89271347	*ABCG2*	non-synonymous coding	0.11	T	0.28	1.9×10^{-44}
Urate	rs2051541	6	25934098	*SLC17A1* / *SLC17A3*	Intergenic	0.50	A	-0.12	1.4×10^{-11}
Urate	rs10792443	11	64147733	*NRXN2*, *SLC22A11*	Intronic	0.73	C	-0.11	8.3×10^{-08}
Gout	rs2231142	4	89271347	*ABCG2*	non-synonymous coding	0.11	T	0.54	3.1×10^{-10}

(No significant findings were obtained from African Americans from the IBC chip.)

Supplementary Table 4 - Best SNPs in African Americans (AA) for known loci related to urate levels in European ancestry individuals

Best SNP at each locus is shown below.

Chr	Gene / Region (1)	Best SNP in AA in the region (2)	Position (b36)	Gene within 50kb	LD (r2/D') in YRI between Best SNP in AA and SNP in EA (rel 22)	Coded Allele	Coded allele frequency	Beta	p-value	# of independent SNPs in queried region (3)	Bonferroni correction threshold	Replication Beta	Replication *P*-value	Meta-analysis Beta	Meta-analysis *P*-value
1	*PDZK1*	rs882211	144444025	*PDZK1*	0.57/1	C	0.80	0.17	1.90×10^{-05}	6	8.33×10^{-03}				
2	*GCKR*, *GTF3C2*, *RBKS*	rs814295	27596719	*GCKR*	0.04/1	A	0.77	-0.04	1.84×10^{-01}	8	6.25×10^{-03}				
		rs11689803	27420024	*GTF3C2*	na/na	A	0.06	-0.20	2.50×10^{-03}	27	1.85×10^{-03}				
		rs9679543	27904455	*RBKS*	0.06/0.83	T	0.53	0.09	8.27×10^{-04}	27	1.85×10^{-03}	-0.01	7.61×10^{-01}	0.07	4.79×10^{-03}
4	*SLC2A9*	rs13129697	9536065	*SLC2A9*	0.79/1	T	0.42	0.32	3.81×10^{-32}	25	2.00×10^{-03}				
4	*SLC2A9*	rs7663032	9602936	*SLC2A9*	0.27/1	T	0.67	0.32	1.17×10^{-30}	25	2.00×10^{-03}				
4	*ABCG2*	rs2869736	89357401	*ABCG2*	0.01/1	T	0.72	-0.10	1.13×10^{-03}	19	2.63×10^{-03}				
6	*RREB1*	rs9505089	7183243	*RREB1*	0.003/0.09	A	0.85	-0.19	5.24×10^{-06}	28	1.79×10^{-03}				
6	*LRRC16*	rs9467527	25602089	*LRRC16*	0.01/1	T	0.93	-0.20	2.71×10^{-04}	63	7.94×10^{-04}				
6	*SLC17A1*, *SLC17A3*	rs11751616	25978521	*SLC17A3*	na/na	A	0.97	0.34	8.72×10^{-03}	17	2.94×10^{-03}				
10	*SLC16A9*	rs11006670	61094672	*SLC16A9*	0.01/1	T	0.06	0.17	1.76×10^{-02}	30	1.67×10^{-03}				
11	*SLC22A11*,	rs12294207	64095162	*SLC22A11*	0.37/0.9	A	0.38	0.11	4.53×10^{-05}	10	5.00×10^{-03}				
11	*SLC22A12*, *NRXN2*, *RASGRP2*, *PYGM*, *SF1*	rs528211	64108297	*SLC22A12*	1/1	T	0.68	0.14	3.92×10^{-06}	8	6.25×10^{-03}				
		rs12800450	64115797	*SLC22A12*	0.03/1	T	0.01	-1.21	4.04×10^{-14}	8	6.25×10^{-03}	-1.08	4.96×10^{-03}	-1.19	2.661×10^{-16}

		rs589691	64281792	*PYGM*	0.06/0.28	T	0.30	-0.17	1.59×10^{-07}	22	2.27×10^{-03}	-0.08	1.33×10^{-01}	-0.15	9.061×10^{-08}
		rs606458	64302967	*SF1*	0.09/0.35	T	0.35	-0.21	2.13×10^{-10}	22	2.27×10^{-03}	-0.11	3.93×10^{-02}	-0.18	5.512×10^{-11}
		rs493573	64313630	*MAP4K2*	0.13/1	T	0.03	-0.81	1.29×10^{-13}	22	2.27×10^{-03}	-0.74	6.90×10^{-05}	-0.80	1.857×10^{-17}
12	*R3HDM2*	rs1106766	56095723	*R3HDM2*	1/1	T	0.09	-0.16	6.46×10^{-04}	28	1.79×10^{-03}				

(1) The gene region was defined as within 50kb of the gene, except when the haplotype block in CEU in HapMap extended further, then the region included up to a recombination hotspot or 500kb on both sides of the gene. The *SLC22A22* region spanned 367kb from 63976kb to 64343kb between recombination hot spots of around 15cM/Mb and 20cM/Mb.

The *GCKR* region spanned 900kb from 27200kb to 28100kb between recombination spot of ~10cM/Mb to 500kb to the right of the reported SNP in EA (rs780094)

(2)The best SNPs are the SNP with the lowest p-value within 50kb of the gene. When the region extends beyond the gene, the best SNPs also include the SNPs with the lowest p-values in the region and having r-square < 0.2 with each other.

(3) We calculate the number of independent SNPs in the ARIC study using pair-wise variance inflation factor threshold of 2, window size of 50 and a shift of 5 SNPs per window.

Supplementary Table 5 - Genotyping and Imputation Platforms

	Array type	Genotype calling	QC filters for genotyped SNPs used for imputation	No of SNPs used for imputation	Imputation	Imputation Backbone for phased CEU haplotypes (NCBI build)	Filtering of imputed genotypes	Data management and statistical analysis
Stage 1:								
CARE Consortium	Affymetrix 6.0	Birdseed v1.33	all chip QC + pi_hat 0.05 for rate step	763537 to 846628	MACH, 2 rounds	combined CEU+YRI reference panel	MAF 1%, rsq_hat 0.3	plink –-dosage
	IBC Chip	Birdseed v1.33	all chip QC + pi_hat 0.05 for rate step	44487 to 46438	MACH, 2 rounds	CEU HapMap 2; combined CEU+YRI reference panel	MAF 1%, rsq_hat 0.4	plink –-dosage; R-LME/GEE (for FHS)
Stage 2: Replication								
HANDLS	Illumina 1M, 1Mduo, 550K, 370K, 510S, and 240S arrays	Beadstudio	HWE p-value > 1e-7, missing by haplotype p-values > 1e-7, minor allele frequency > 0.01,	907763	MACHv1.0.16	HapMap Phase II YRI and CEU samples	MAF 1%, rsq_hat 0.3	R,PLINK,RELPAIR,MACH2
HUFS	Affymetrix 6.0	Birdseed v2	MAF 1%, SNP call rate 95%, sample call rate 95%	842152	MACH v1.0.16	Phase II+III CEU and YRI HapMap	MAF 1%, SNP call rate 90%, HWE 1e-3, genotypic concordance 95%	PLINK, R

Supplementary Table 6 - SNP Imputation Quality

SNP	ARIC	CARDIA	CHS	JHS	FHS	Median Imputation Quality	Platform	Ethnicity (1)	Trait	HANDLS	HUFS
rs9321453	1.00	1.04	NA	1.00	NA	1.00	Affy 6.0	AA	Urate		
rs10792443	0.41	0.41	0.41	NA	0.43	0.41	IBC	EA	Urate		
rs11172147	0.84	0.80	0.80	NA	0.79	0.80	IBC	EA	Urate		
rs1260326	0.98	0.98	0.99	NA	0.99	0.99	IBC	EA	Urate		
rs2051541	0.52	0.53	0.51	NA	0.52	0.52	IBC	EA	Urate		
rs2231142	0.99	0.96	1.03	NA	1.00	0.99	IBC	EA	Urate, gout		
rs2241480	0.47	0.49	0.46	NA	0.44	0.47	IBC	EA	Urate		
rs11006670	0.72	0.66	NA	0.71	NA	0.71	Affy 6.0	AA	Urate		
rs1106766	1.02	1.00	NA	1.01	NA	1.01	Affy 6.0	AA	Urate		
rs1165205	0.99	1.05	NA	0.96	NA	0.99	Affy 6.0	AA	Urate		
rs11689803	0.84	0.82	NA	0.80	NA	0.82	Affy 6.0	AA	Urate		
rs11751616	0.40	0.41	NA	0.41	NA	0.41	Affy 6.0	AA	Urate		
rs1183201	0.99	1.05	NA	0.95	NA	0.99	Affy 6.0	AA	Urate		
rs12129861	0.94	0.93	NA	0.90	NA	0.93	Affy 6.0	AA	Urate		
rs12294207	0.96	1.02	NA	1.02	NA	1.02	Affy 6.0	AA	Urate		
rs12356193	0.71	0.74	NA	0.75	NA	0.74	Affy 6.0	AA	Urate		
rs12800450	0.52	0.50	NA	0.53	NA	0.52	Affy 6.0	AA	Urate	0.61	NA
rs13129697	0.97	0.99	NA	1.01	NA	0.99	Affy 6.0	AA	Urate		
rs16890979	0.97	0.88	NA	1.00	NA	0.97	Affy 6.0	AA	Urate		
rs17300741	0.87	0.87	NA	0.91	NA	0.87	Affy 6.0	AA	Urate		
rs2096386	0.99	1.01	NA	0.97	NA	0.99	Affy 6.0	AA	Urate		
rs2869736	0.89	0.92	NA	0.86	NA	0.89	Affy 6.0	AA	Urate		
rs4148155	0.93	0.94	NA	0.88	NA	0.93	Affy 6.0	AA	Urate		
rs493573	0.57	0.54	NA	0.58	NA	0.57	Affy 6.0	AA	Urate	0.99	0.51
rs505802	0.99	1.06	NA	0.96	NA	0.99	Affy 6.0	AA	Urate		

rs528211	0.95	1.03	NA	0.96	NA	0.96	Affy 6.0	AA	Urate		
rs589691	0.89	0.91	NA	0.90	NA	0.90	Affy 6.0	AA	Urate	(2)	0.81
rs606458	0.76	0.81	NA	0.79	NA	0.79	Affy 6.0	AA	Urate	(2)	0.80
rs6449213	1.01	1.00	NA	0.98	NA	1.00	Affy 6.0	AA	Urate		
rs675209	0.87	0.89	NA	0.88	NA	0.88	Affy 6.0	AA	Urate		
rs734553	0.96	0.96	NA	1.02	NA	0.96	Affy 6.0	AA	Urate		
rs742132	0.97	1.05	NA	0.98	NA	0.98	Affy 6.0	AA	Urate		
rs7663032	1.00	1.00	NA	1.02	NA	1.00	Affy 6.0	AA	Urate		
rs780094	1.01	0.99	NA	0.96	NA	0.99	Affy 6.0	AA	Urate		
rs814295	0.98	0.97	NA	0.94	NA	0.97	Affy 6.0	AA	Urate		
rs882211	0.71	0.72	NA	0.70	NA	0.71	Affy 6.0	AA	Urate		
rs9321453	1.00	1.04	NA	1.00	NA	1.00	Affy 6.0	AA	Urate	0.98	0.99
rs9467527	0.95	0.94	NA	0.88	NA	0.94	Affy 6.0	AA	Urate		
rs9505089	0.86	0.83	NA	0.87	NA	0.86	Affy 6.0	AA	Urate		
rs9679543	1.03	1.01	NA	0.95	NA	1.01	Affy 6.0	AA	Urate	0.99	0.98

(1) AA: African American Ancestry; EA: European Ancestry
(2) Genotype call rate > 0.99

Supplementary Table 7: All genome-wide (P-Value <5x10^{-8}) and IBC-wide (P-Value<2x10^{-6}) Significant SNP Associations with MAF > 1%

Supplementary Table 7A: Serum urate, Affy 6.0, African Americans, pvalue < 5x10^{-8} and MAF > 1%							
SNP ID	Coded Allele	Noncoded Allele	Beta	SE	P-value	Chr	Position
rs13129697	T	G	0.32	0.03	3.81E-32	4	9536065
rs7663032	T	C	0.32	0.03	1.17E-30	4	9602936
rs3775948	C	G	0.32	0.03	1.68E-30	4	9604280
rs938558	A	G	0.30	0.03	2.78E-30	4	9548303
rs10939650	T	C	0.32	0.03	1.09E-29	4	9607538
rs13113918	A	G	-0.35	0.03	1.23E-29	4	9607591
rs3733588	A	G	0.32	0.03	4.22E-29	4	9606401
rs12498742	A	G	0.30	0.03	8.62E-29	4	9553150
rs4529048	A	C	0.31	0.03	1.29E-28	4	9606210
rs10805346	T	C	0.30	0.03	5.19E-28	4	9529445
rs7675964	T	C	-0.29	0.03	5.88E-28	4	9550532
rs16868246	C	G	-0.30	0.03	1.26E-27	4	9587403
rs13131257	T	C	-0.30	0.03	3.25E-27	4	9590987
rs11722229	A	C	0.29	0.03	3.41E-27	4	9589795
rs1071988	A	G	0.30	0.03	3.54E-27	4	9583736
rs6838021	T	C	-0.28	0.03	1.45E-25	4	9536718
rs1014290	A	G	0.30	0.03	2.57E-25	4	9610959
rs737267	T	G	-0.27	0.03	2.05E-24	4	9543842
rs7670751	A	C	0.27	0.03	2.11E-24	4	9547871
rs9991278	T	C	-0.34	0.03	2.26E-24	4	9611763

rs734553	T	G	0.28	0.03	2.68E-24	4	9532102
rs6855911	A	G	0.27	0.03	4.40E-24	4	9545008
rs938564	T	G	0.27	0.03	4.51E-24	4	9531671
rs4697701	A	G	-0.26	0.03	8.17E-23	4	9555193
rs5028843	A	G	-0.26	0.03	1.30E-22	4	9549904
rs10022499	A	C	0.26	0.03	4.60E-22	4	9615635
rs9291640	T	C	0.26	0.03	5.08E-22	4	9616184
rs6832439	A	G	-0.26	0.03	6.43E-22	4	9533417
rs10023068	A	G	-0.26	0.03	1.13E-21	4	9613930
rs6853437	A	G	0.26	0.03	2.46E-21	4	9614533
rs7660895	A	G	-0.26	0.03	5.62E-21	4	9594543
rs13145758	A	G	0.25	0.03	4.08E-20	4	9591095
rs938554	C	G	-0.25	0.03	5.04E-19	4	9534790
rs938555	A	G	-0.25	0.03	5.50E-19	4	9535149
rs16891971	A	C	-0.34	0.04	2.07E-18	4	9607474
rs882223	A	C	-0.28	0.03	2.10E-18	4	9590723
rs11723970	T	C	-0.28	0.03	2.42E-18	4	9589560
rs16890979	T	C	-0.24	0.03	2.53E-18	4	9531265
rs7669607	T	C	-0.30	0.03	2.79E-18	4	9606899
rs4235346	T	C	-0.27	0.03	5.85E-18	4	9554394
rs874432	A	T	-0.24	0.03	6.02E-18	4	9529704
rs4292328	T	C	-0.27	0.03	6.54E-18	4	9580060
rs714873	A	G	0.26	0.03	7.28E-18	4	9668716
rs6826764	C	G	0.28	0.03	8.13E-18	4	9639892
rs7375599	A	G	0.27	0.03	8.28E-18	4	9564016
rs10006397	A	C	0.27	0.03	8.33E-18	4	9645238
rs4447863	T	C	0.28	0.03	9.25E-18	4	9548067

rs4697698	T	C	0.27	0.03	1.95E-17	4	9551675
rs733175	T	C	0.26	0.03	2.67E-17	4	9659239
rs7349721	A	T	-0.27	0.03	6.48E-17	4	9651660
rs6849717	T	C	0.26	0.03	1.22E-16	4	9567817
rs13103690	T	G	0.26	0.03	1.52E-16	4	9581876
rs7439210	C	G	0.23	0.03	2.07E-16	4	9580847
rs11942223	T	C	0.23	0.03	3.51E-16	4	9571863
rs13111638	T	C	-0.32	0.04	3.65E-16	4	9605988
rs7442295	A	G	0.22	0.03	4.01E-16	4	9575478
rs13115193	T	C	0.26	0.03	4.22E-16	4	9591289
rs11723591	A	T	0.26	0.03	5.58E-16	4	9594496
rs6449173	T	G	0.22	0.03	7.34E-16	4	9575203
rs12499857	A	G	0.26	0.03	8.15E-16	4	9604474
rs4697700	C	G	-0.22	0.03	1.06E-15	4	9554890
rs4475146	A	C	-0.22	0.03	1.50E-15	4	9555754
rs4697695	A	G	0.23	0.03	1.99E-15	4	9524948
rs6834555	A	G	0.25	0.03	3.21E-15	4	9671424
rs17246501	A	C	-0.24	0.03	1.15E-14	4	9594808
rs6449213	T	C	0.29	0.04	2.84E-14	4	9603313
rs12800450	T	G	-1.21	0.16	4.04E-14	11	64115797
rs11722228	T	C	0.23	0.03	4.17E-14	4	9524839
rs998675	T	C	-0.24	0.03	4.92E-14	4	9557927
rs17247314	C	G	-0.25	0.03	5.34E-14	4	9613841
rs3775942	A	G	-0.26	0.03	5.99E-14	4	9629405
rs13122112	A	G	-0.26	0.03	7.00E-14	4	9630502
rs2240723	A	G	-0.26	0.03	7.70E-14	4	9630249
rs9998811	A	G	-0.23	0.03	1.01E-13	4	9575575

rs3775939	C	G	0.26	0.03	1.02E-13	4	9634394
rs13106922	A	G	0.26	0.03	1.12E-13	4	9630857
rs1122141	T	C	0.24	0.03	1.28E-13	4	9556376
rs3775941	A	T	-0.25	0.03	1.42E-13	4	9634191
rs6856396	A	T	-0.26	0.04	2.62E-13	4	9640261
rs2240721	A	G	0.23	0.03	6.67E-13	4	9629662
rs881971	T	C	0.21	0.03	1.30E-12	4	9540060
rs7678012	T	C	-0.20	0.03	3.87E-12	4	9602870
rs4320137	T	C	0.26	0.04	4.06E-12	4	9682067
rs7680126	A	G	0.30	0.04	4.45E-12	4	9594694
rs3796842	A	T	-0.20	0.03	4.91E-12	4	9604949
rs12506455	A	T	0.22	0.03	7.73E-12	4	9640667
rs11722930	A	G	0.22	0.03	8.31E-12	4	9644552
rs11731110	T	C	-0.22	0.03	8.66E-12	4	9646444
rs3733585	A	G	-0.22	0.03	8.69E-12	4	9645437
rs10939665	T	C	-0.22	0.03	8.76E-12	4	9646726
rs11727199	T	C	0.22	0.03	8.81E-12	4	9645288
rs3756236	A	T	0.22	0.03	9.47E-12	4	9622561
rs13133766	T	C	0.22	0.03	1.09E-11	4	9628830
rs2240720	T	C	0.22	0.03	1.11E-11	4	9629578
rs7679916	T	C	0.22	0.03	1.23E-11	4	9651258
rs12508991	T	C	0.22	0.03	1.30E-11	4	9650202
rs2240724	C	G	0.22	0.03	1.35E-11	4	9630388
rs7376960	A	G	0.28	0.04	1.66E-11	4	9579668
rs13101785	A	T	0.22	0.03	1.74E-11	4	9652013
rs13137343	A	C	0.22	0.03	1.77E-11	4	9652126
rs10939669	A	G	-0.22	0.03	1.96E-11	4	9654925

rs13103879	T	C	0.20	0.03	2.79E-11	4	9581977
rs7663097	T	C	0.20	0.03	3.71E-11	4	9575889
rs4698036	T	G	0.24	0.04	3.81E-11	4	9940392
rs4292327	A	G	0.22	0.03	5.02E-11	4	9552798
rs17187075	C	G	0.20	0.03	1.10E-10	4	9599426
rs7683832	A	G	-0.22	0.03	1.19E-10	4	9665180
rs606458	T	C	-0.21	0.03	2.13E-10	11	64302967
rs6449202	T	C	0.19	0.03	2.82E-10	4	9583141
rs6847019	T	C	0.20	0.03	3.14E-10	4	9575347
rs6449175	T	C	-0.20	0.03	3.16E-10	4	9575708
rs12499240	T	C	0.17	0.03	3.69E-10	4	9712988
rs4505821	A	G	0.20	0.03	4.12E-10	4	9587192
rs16891234	T	C	-0.21	0.03	4.14E-10	4	9555261
rs4481233	T	C	-0.29	0.05	4.43E-10	4	9565177
rs10033612	T	C	0.20	0.03	4.44E-10	4	9594104
rs7435196	A	C	0.18	0.03	6.06E-10	4	9576654
rs4385059	T	C	0.29	0.05	6.25E-10	4	9598331
rs7375587	A	T	0.18	0.03	6.28E-10	4	9563856
rs6821843	A	C	-0.22	0.04	7.09E-10	4	9661626
rs16892475	A	C	0.23	0.04	7.29E-10	4	9649371
rs10003001	T	C	0.20	0.03	7.42E-10	4	9593573
rs4697913	T	C	-0.20	0.03	7.71E-10	4	9550360
rs6823361	A	G	0.18	0.03	7.84E-10	4	9572225
rs6449157	A	G	-0.18	0.03	7.95E-10	4	9569540
rs11724510	T	C	-0.18	0.03	8.15E-10	4	9567681
rs13135351	A	G	-0.24	0.04	1.03E-09	4	9642623
rs3796840	T	C	-0.32	0.05	1.05E-09	4	9617219

rs10939681	A	C	0.21	0.04	1.14E-09	4	9665062
rs4697926	A	C	0.20	0.03	1.14E-09	4	9733665
rs16892419	A	C	-0.23	0.04	1.16E-09	4	9644800
rs12642537	A	G	-0.23	0.04	1.48E-09	4	9646719
rs16892420	A	G	-0.23	0.04	1.48E-09	4	9644813
rs3822250	T	C	-0.23	0.04	1.52E-09	4	9645728
rs10939679	T	C	0.21	0.04	1.58E-09	4	9664953
rs12499734	T	C	-0.22	0.04	1.96E-09	4	9660859
rs16892474	A	C	-0.23	0.04	2.06E-09	4	9649318
rs11723439	T	C	-0.28	0.05	2.27E-09	4	9560917
rs10516197	T	C	-0.23	0.04	2.35E-09	4	9651198
rs16892493	T	C	-0.23	0.04	2.36E-09	4	9650745
rs7699671	T	C	-0.19	0.03	2.37E-09	4	9734972
rs10516196	T	C	-0.23	0.04	2.51E-09	4	9650063
rs4393994	T	C	-0.16	0.03	2.54E-09	4	9724219
rs3822236	T	G	0.19	0.03	3.70E-09	4	9729059
rs1079128	T	C	0.17	0.03	7.10E-09	4	9560319
rs9321453	T	C	0.15	0.03	1.39E-08	6	134815247
rs4622999	C	G	-0.17	0.03	1.42E-08	4	9612493
rs4697708	T	C	0.19	0.03	1.81E-08	4	9730287
rs6849736	A	G	-0.22	0.04	1.81E-08	4	9595881
rs3733590	T	C	0.22	0.04	1.94E-08	4	9596324
rs4235355	A	C	-0.18	0.03	2.39E-08	4	9732176
rs4697710	T	C	0.18	0.03	2.53E-08	4	9731747
rs2139243	A	G	0.15	0.03	2.80E-08	4	9476600
rs3756231	A	G	0.22	0.04	4.74E-08	4	9634642

Supplementary Table 7B: IBC-wide significant SNP Association							
Serum urate, IBC Chip, European Americans, P-value < $2x10^{-6}$ and MAF > 1%							
SNP ID	Coded Allele	Noncoded Allele	Beta	SE	P-value	Chr	Position
rs4148155	A	G	-0.28	0.02	1.15E-44	4	89273691
rs2199936	A	G	0.29	0.02	1.72E-44	4	89264355
rs2231142	T	G	0.28	0.02	1.91E-44	4	89271347
rs1481012	A	G	-0.29	0.02	1.44E-43	4	89258106
rs2241480	T	C	0.22	0.02	2.26E-29	4	9698861
rs2241470	T	G	-0.22	0.02	2.46E-29	4	9693668
rs6830786	T	C	0.22	0.02	2.47E-29	4	9710541
rs11731597	T	C	0.23	0.02	2.72E-29	4	9684583
rs734122	A	G	0.22	0.02	2.78E-29	4	9698963
rs10516200	A	C	0.22	0.02	2.80E-29	4	9691254
rs2241486	C	G	-0.21	0.02	3.00E-29	4	9710181
rs16868326	A	T	0.21	0.02	3.17E-29	4	9711691
rs9926	A	G	0.21	0.02	5.90E-29	4	9685958
rs3796818	T	C	0.20	0.02	6.37E-29	4	9707074
rs6449286	A	T	0.19	0.02	6.59E-29	4	9735797
rs3756230	C	G	-0.20	0.02	7.10E-29	4	9692927
rs2241488	T	C	-0.19	0.02	7.23E-29	4	9710229
rs4467562	A	G	0.19	0.02	7.81E-29	4	9736239
rs3756227	A	C	0.21	0.02	7.90E-29	4	9697093
rs10001106	T	C	-0.19	0.02	8.06E-29	4	9736539
rs2241468	A	G	0.19	0.02	1.38E-28	4	9723003
rs3756215	A	G	-0.16	0.01	1.63E-28	4	9730358

rs6825888	T	C	-0.16	0.01	1.79E-28	4	9731832
rs3886038	T	C	0.16	0.01	1.84E-28	4	9734353
rs6827496	A	G	-0.24	0.02	1.97E-28	4	9760754
rs4619888	A	C	-0.17	0.02	1.98E-28	4	9736076
rs10516201	T	C	-0.16	0.01	2.02E-28	4	9733039
rs4456954	C	G	0.26	0.02	2.04E-28	4	9733936
rs715979	C	G	-0.17	0.02	2.19E-28	4	9734340
rs12506893	T	C	0.16	0.01	2.19E-28	4	9732763
rs881641	A	G	0.20	0.02	2.20E-28	4	9742845
rs1109472	C	G	0.20	0.02	2.24E-28	4	9743546
rs715260	C	G	-0.17	0.02	2.32E-28	4	9737244
rs17197769	T	C	0.20	0.02	2.34E-28	4	9743434
rs12502556	C	G	-0.20	0.02	2.38E-28	4	9739603
rs6449300	T	C	0.20	0.02	2.49E-28	4	9748649
rs12507725	A	T	0.20	0.02	2.50E-28	4	9746888
rs12501597	T	G	0.20	0.02	2.98E-28	4	9741235
rs881643	A	G	0.20	0.02	3.06E-28	4	9743215
rs17198113	T	C	0.21	0.02	3.07E-28	4	9747568
rs6813334	T	G	-0.23	0.02	3.08E-28	4	9757851
rs881642	T	C	0.20	0.02	3.20E-28	4	9742971
rs7667775	T	C	0.19	0.02	3.22E-28	4	9737634
rs12507586	A	G	0.23	0.02	3.23E-28	4	9757673
rs11938608	T	C	-0.20	0.02	3.38E-28	4	9744947
rs12508413	A	G	0.23	0.02	3.43E-28	4	9757769
rs2054576	A	G	-0.23	0.02	3.84E-27	4	89247799
rs4148157	A	G	0.23	0.02	1.17E-26	4	89239958
rs2728126	A	T	0.24	0.02	2.14E-26	4	89218246

rs2728125	A	G	-0.23	0.02	2.19E-26	4	89220917
rs2728121	T	C	0.26	0.02	9.33E-25	4	89216126
rs2728099	T	C	-0.30	0.03	2.26E-24	4	89194762
rs2728104	T	C	-0.26	0.03	3.76E-24	4	89192030
rs2725211	T	C	0.27	0.03	5.04E-24	4	89189399
rs2725215	T	C	0.27	0.03	8.49E-24	4	89180595
rs2231164	T	C	-0.18	0.02	1.54E-23	4	89234881
rs2728109	A	C	0.27	0.03	5.08E-23	4	89176747
rs2728113	A	G	-0.27	0.03	1.76E-22	4	89158760
rs2725234	T	C	0.27	0.03	3.20E-22	4	89151296
rs2725203	T	C	-0.23	0.02	4.20E-21	4	89214819
rs4336187	A	G	-0.23	0.02	4.73E-21	4	89206940
rs2725205	A	G	0.23	0.02	4.75E-21	4	89204735
rs2728132	A	C	-0.24	0.03	5.10E-21	4	89201485
rs2725207	A	C	0.24	0.03	5.46E-21	4	89198553
rs2728133	T	C	-0.24	0.03	5.46E-21	4	89200714
rs2725210	A	G	-0.24	0.03	6.74E-21	4	89192451
rs11730059	A	G	0.28	0.03	7.02E-21	4	89106351
rs2728106	A	G	0.24	0.03	7.86E-21	4	89191075
rs2622621	C	G	-0.12	0.01	1.32E-18	4	89249944
rs2622605	T	C	-0.12	0.01	3.72E-18	4	89298410
rs3114020	T	C	-0.12	0.01	4.03E-18	4	89302690
rs2728119	A	G	-0.23	0.03	1.48E-16	4	89096555
rs17731799	T	G	0.10	0.01	2.14E-16	4	89287479
rs2622624	T	C	-0.10	0.01	2.20E-16	4	89288430
rs2622626	A	C	0.10	0.01	1.03E-15	4	89285739
rs3114018	A	C	-0.09	0.01	7.28E-14	4	89283605

rs1260326	T	C	0.09	0.01	7.66E-14	2	27584444
rs780094	T	C	0.09	0.01	6.44E-13	2	27594741
rs780093	T	C	0.09	0.01	7.49E-13	2	27596107
rs12513376	T	C	0.22	0.03	2.36E-12	4	9765320
rs2728110	A	G	-0.11	0.02	2.38E-12	4	89171907
rs2725225	T	C	-0.11	0.02	2.61E-12	4	89171100
rs2725227	T	C	0.11	0.02	3.02E-12	4	89163535
rs1260333	A	G	0.09	0.01	6.36E-12	2	27602128
rs2911711	A	T	-0.09	0.01	6.99E-12	2	27604050
rs2051541	A	G	-0.12	0.02	1.40E-11	6	26053190
rs17013584	A	G	0.17	0.02	2.54E-11	4	89091987
rs12505410	T	G	0.09	0.01	4.60E-11	4	89249865
rs2467052	T	G	0.11	0.02	6.70E-11	4	89168199
rs115810	C	G	0.12	0.02	1.35E-10	6	26083862
rs199753	A	G	0.12	0.02	1.50E-10	6	26109867
rs199752	T	C	0.11	0.02	1.51E-10	6	26120854
rs199751	T	C	-0.11	0.02	1.61E-10	6	26123562
rs199750	T	C	0.11	0.02	1.61E-10	6	26124441
rs2728116	A	C	0.11	0.02	1.70E-10	4	89150074
rs9467664	A	T	-0.11	0.02	1.70E-10	6	26129792
rs1540276	T	G	-0.11	0.02	1.74E-10	6	26136798
rs2230655	A	G	0.10	0.02	1.82E-10	6	26141485
rs2213284	A	G	0.10	0.02	1.91E-10	6	26139847
rs1540275	T	C	-0.10	0.02	1.94E-10	6	26144455
rs1150660	A	C	-0.10	0.02	1.98E-10	6	26209419
rs198853	T	C	0.10	0.02	1.99E-10	6	26212075
rs12346	T	C	-0.10	0.02	2.04E-10	6	26205025

rs807212	A	G	-0.10	0.02	2.20E-10	6	26173600
rs13120400	T	C	0.08	0.01	3.25E-10	4	89252551
rs9393676	A	G	0.11	0.02	3.60E-10	6	26044923
rs9295678	A	G	0.11	0.02	3.62E-10	6	26045012
rs9358901	T	G	0.10	0.02	8.54E-10	6	26132415
rs2622604	T	C	-0.09	0.01	8.59E-10	4	89297948
rs4401650	A	G	0.10	0.02	9.34E-10	6	26143187
rs7756117	A	G	0.10	0.02	1.01E-09	6	26154544
rs807214	C	G	0.09	0.02	1.86E-09	6	26169748
rs3109823	T	C	0.08	0.01	2.16E-09	4	89283626
rs7749342	T	C	-0.11	0.02	2.33E-09	6	26028244
rs556339	T	C	0.12	0.02	2.97E-09	6	25978724
rs1165158	A	C	0.12	0.02	3.45E-09	6	25972877
rs1165159	A	G	-0.12	0.02	3.71E-09	6	25972604
rs1165161	T	C	0.12	0.02	3.74E-09	6	25972341
rs1165162	T	C	0.12	0.02	3.85E-09	6	25971584
rs1165167	A	G	-0.12	0.02	4.05E-09	6	25968667
rs1182814	T	C	-0.12	0.02	4.25E-09	6	25967533
rs1165187	T	C	-0.12	0.02	4.92E-09	6	25959348
rs1165189	A	C	-0.12	0.02	5.10E-09	6	25957758
rs603089	A	G	0.12	0.02	5.17E-09	6	25985949
rs1165148	T	G	0.12	0.02	5.69E-09	6	25952689
rs1165164	A	G	0.11	0.02	7.38E-09	6	25971460
rs1165165	T	C	0.11	0.02	7.47E-09	6	25970445
rs10425	A	G	-0.09	0.02	7.68E-09	6	26164528
rs2032447	A	G	-0.10	0.02	7.83E-09	6	26152348
rs10011796	T	C	0.08	0.01	1.18E-08	4	89309901

rs10009618	T	C	-0.09	0.02	1.24E-08	4	89313032
rs1481017	T	C	-0.09	0.02	1.25E-08	4	89316501
rs1408268	A	T	0.12	0.02	1.36E-08	6	25934965
rs6456703	T	C	0.12	0.02	1.40E-08	6	25934098
rs13200784	A	T	-0.12	0.02	1.45E-08	6	25937612
rs1179087	T	G	0.11	0.02	1.72E-08	6	25966683
rs198834	A	G	-0.09	0.02	2.50E-08	6	26222351
rs198820	A	G	-0.09	0.02	2.56E-08	6	26232222
rs198815	A	G	0.09	0.02	2.57E-08	6	26235250
rs198852	A	G	0.09	0.02	2.61E-08	6	26212427
rs198845	T	G	-0.09	0.02	2.62E-08	6	26215769
rs198848	T	C	-0.09	0.02	2.62E-08	6	26214304
rs4665987	A	G	0.08	0.01	4.55E-08	2	27609329
rs4666000	T	C	-0.07	0.01	6.12E-08	2	27692873
rs2068834	T	C	-0.07	0.01	6.35E-08	2	27693043
rs4665991	A	G	0.07	0.01	6.48E-08	2	27619788
rs4665382	T	C	-0.07	0.01	7.92E-08	2	27637305
rs10792443	C	G	-0.11	0.02	8.34E-08	11	64151828
rs2360873	C	G	-0.12	0.02	8.48E-08	11	64147733
rs11231845	A	G	-0.11	0.02	8.62E-08	11	64163995
rs10208529	A	T	-0.07	0.01	8.74E-08	2	27639692
rs2666559	T	G	-0.11	0.02	8.80E-08	11	64195803
rs500531	T	G	-0.10	0.02	8.82E-08	11	64243595
rs544838	T	C	0.11	0.02	8.95E-08	11	64185635
rs555456	T	C	0.11	0.02	8.97E-08	11	64174835
rs4665383	C	G	-0.07	0.01	9.24E-08	2	27645059
rs492175	A	G	-0.11	0.02	9.28E-08	11	64189654

rs1919128	A	G	-0.07	0.01	9.29E-08	2	27655263
rs519090	C	G	-0.11	0.02	9.53E-08	11	64212816
rs506338	T	C	0.11	0.02	9.57E-08	11	64197496
rs2071303	T	C	-0.07	0.01	9.68E-08	6	26199315
rs504915	A	T	-0.11	0.02	9.89E-08	11	64220661
rs13022873	A	C	-0.07	0.01	1.16E-07	2	27669014
rs2384656	A	G	-0.07	0.01	1.16E-07	2	27685559
rs1919127	T	C	-0.07	0.01	1.17E-07	2	27654997
rs12478841	A	G	-0.07	0.01	1.17E-07	2	27665226
rs12467476	T	C	-0.07	0.01	1.17E-07	2	27679219
rs6760250	A	G	0.07	0.01	1.18E-07	2	27665756
rs7696304	A	G	0.09	0.02	1.86E-07	4	89179022
rs198806	A	G	0.10	0.02	2.46E-07	6	26241595
rs3749147	A	G	0.07	0.01	2.56E-07	2	27705422
rs6918586	T	C	-0.08	0.02	2.73E-07	6	26205363
rs13002853	C	G	-0.07	0.01	2.76E-07	2	27706749
rs487662	A	G	-0.11	0.02	3.32E-07	11	64238456
rs480617	T	C	-0.11	0.02	3.38E-07	11	64234896
rs10897526	T	C	-0.07	0.01	4.54E-07	11	64316474
rs1466462	C	G	0.06	0.01	8.35E-07	11	65175940
rs10965	A	G	-0.08	0.02	1.62E-06	4	89217107
rs11938025	A	T	0.08	0.02	1.93E-06	4	89206300
Supplementary Table 7C: IBC-wide significant SNP Association							
Gout, IBC chip, European Americans, pvalue < $2x10^{-6}$ and MAF > 1%							
SNP ID	Coded Allele	Noncoded Allele	Beta	SE	P-value	Chr	Position

rs1481012	A	G	-0.57	0.09	1.80E-10	4	89258106
rs4148155	A	G	-0.55	0.09	2.73E-10	4	89273691
rs2231142	T	G	0.54	0.09	3.13E-10	4	89271347
rs2199936	A	G	0.55	0.09	4.02E-10	4	89264355
rs2728109	A	C	0.69	0.12	1.86E-09	4	89176747
rs2728113	A	G	-0.70	0.12	2.10E-09	4	89158760
rs2725234	T	C	0.71	0.12	2.25E-09	4	89151296
rs2725215	T	C	0.67	0.11	2.90E-09	4	89180595
rs11730059	A	G	0.75	0.13	2.91E-09	4	89106351
rs2725211	T	C	0.66	0.11	2.95E-09	4	89189399
rs2728104	T	C	-0.66	0.11	3.01E-09	4	89192030
rs2728121	T	C	0.62	0.11	3.38E-09	4	89216126
rs2728099	T	C	-0.74	0.13	3.68E-09	4	89194762
rs2728126	A	T	0.55	0.10	8.26E-09	4	89218246
rs2728125	A	G	-0.54	0.09	9.17E-09	4	89220917
rs2728106	A	G	0.63	0.11	1.24E-08	4	89191075
rs2728133	T	C	-0.61	0.11	1.30E-08	4	89200714
rs2725207	A	C	0.61	0.11	1.30E-08	4	89198553
rs2725210	A	G	-0.62	0.11	1.33E-08	4	89192451
rs2728132	A	C	-0.61	0.11	1.36E-08	4	89201485
rs2725205	A	G	0.61	0.11	1.38E-08	4	89204735
rs4336187	A	G	-0.61	0.11	1.41E-08	4	89206940
rs2054576	A	G	-0.52	0.09	1.46E-08	4	89247799
rs2725203	T	C	-0.60	0.11	1.47E-08	4	89214819
rs4148157	A	G	0.52	0.09	1.60E-08	4	89239958
rs2728119	A	G	-0.68	0.12	3.98E-08	4	89096555
rs2231164	T	C	-0.40	0.08	1.04E-06	4	89234881