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Supplementary Table S7A Univariate and multivariate logistic regression including three SNPs of *ABCG2*.

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Supplementary Table S8 Magnitude of gout risk associated with the number of risk alleles.

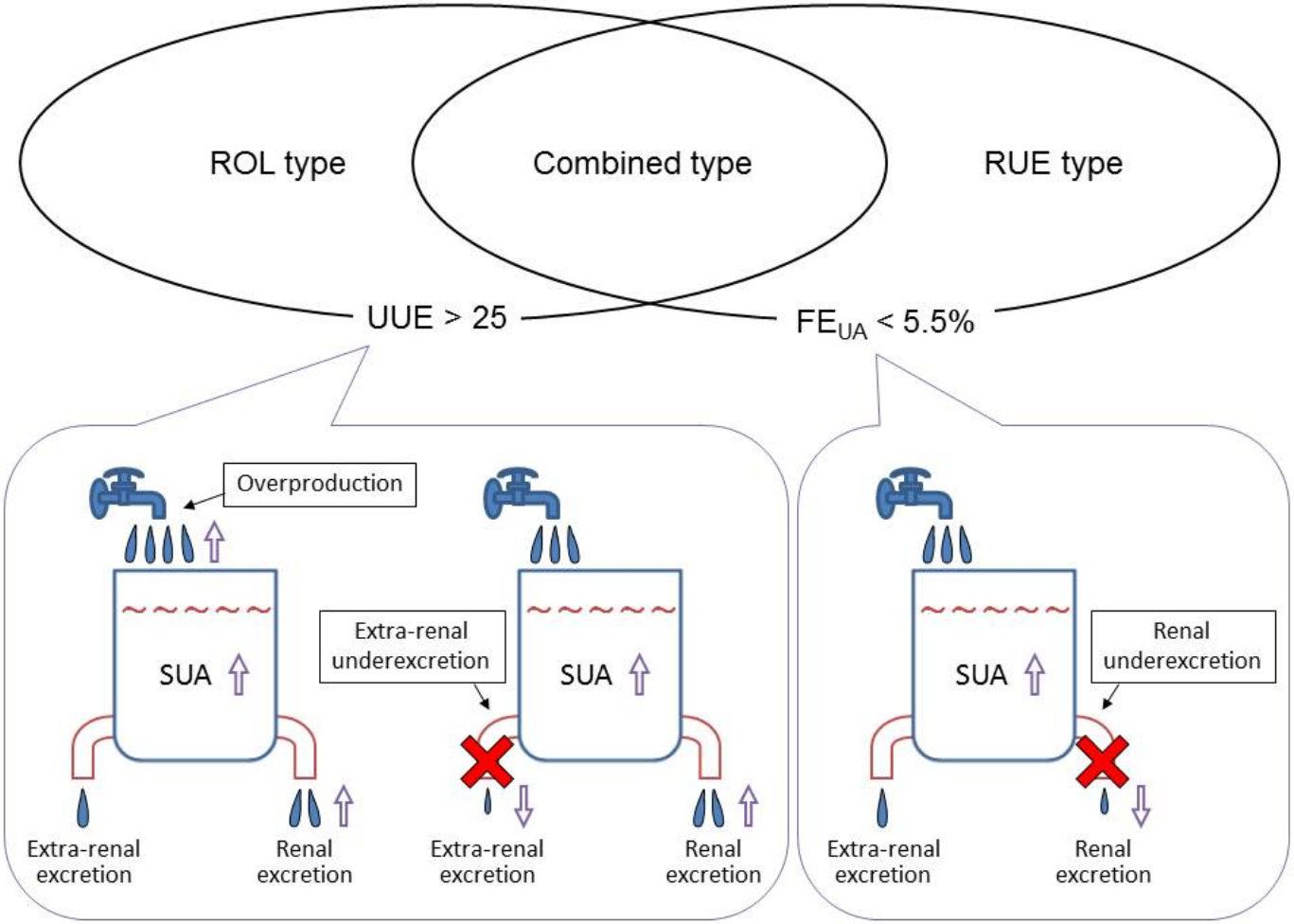
Supplementary Table S9 Association analysis between seven SNPs and three uric acid-related parameters.

Supplementary Table S10 Linkage disequilibrium among rs4073582 of *CNIH-2*, rs10791821 of *MAP3K11*, and rs504915 of *NRXN2.*

Supplementary Table S11 Multivariate logistic regression analysis adjusted with rs504915 of *NRXN2.*

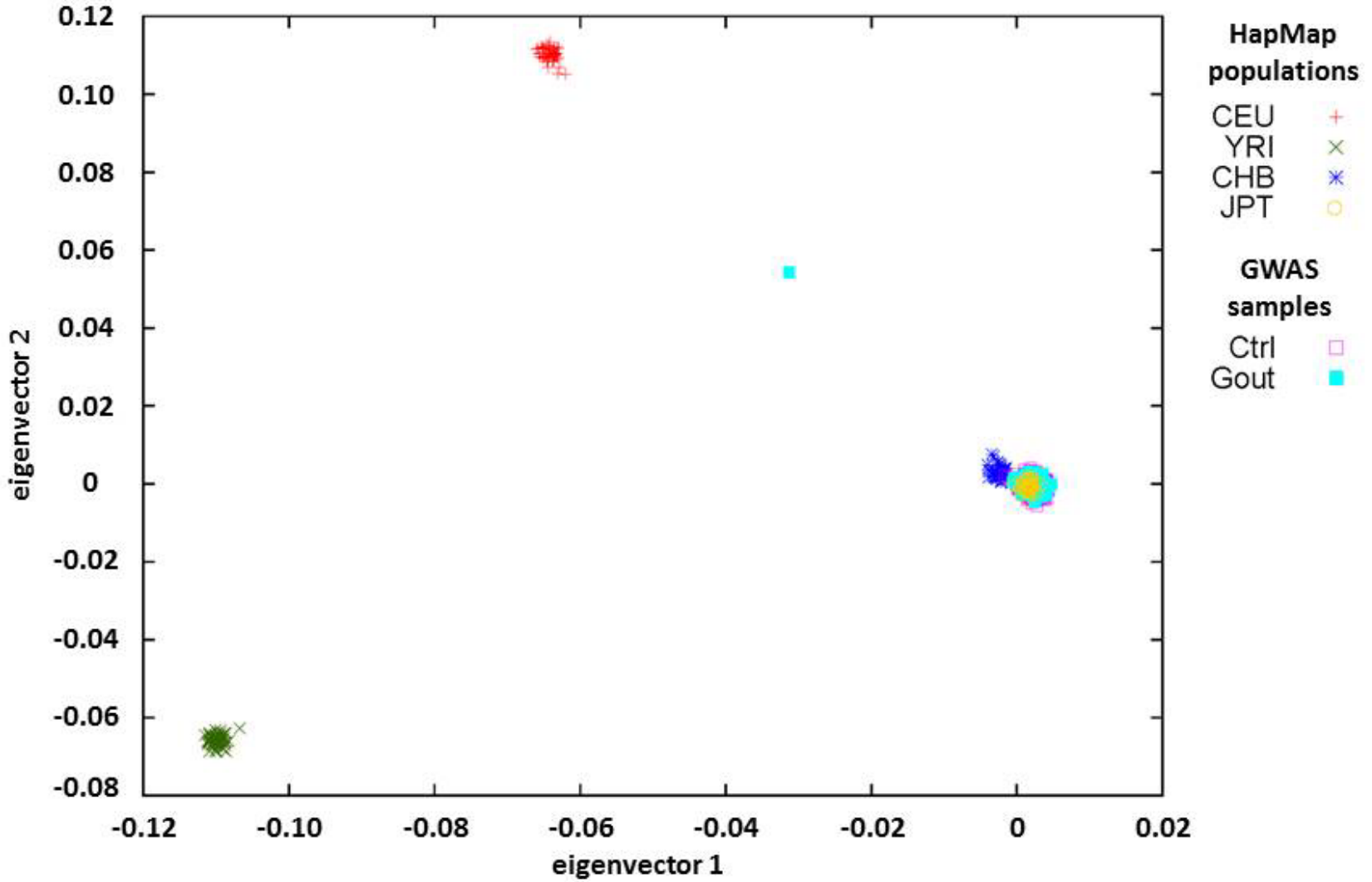
Supplementary Methods

References for Supplementary Methods

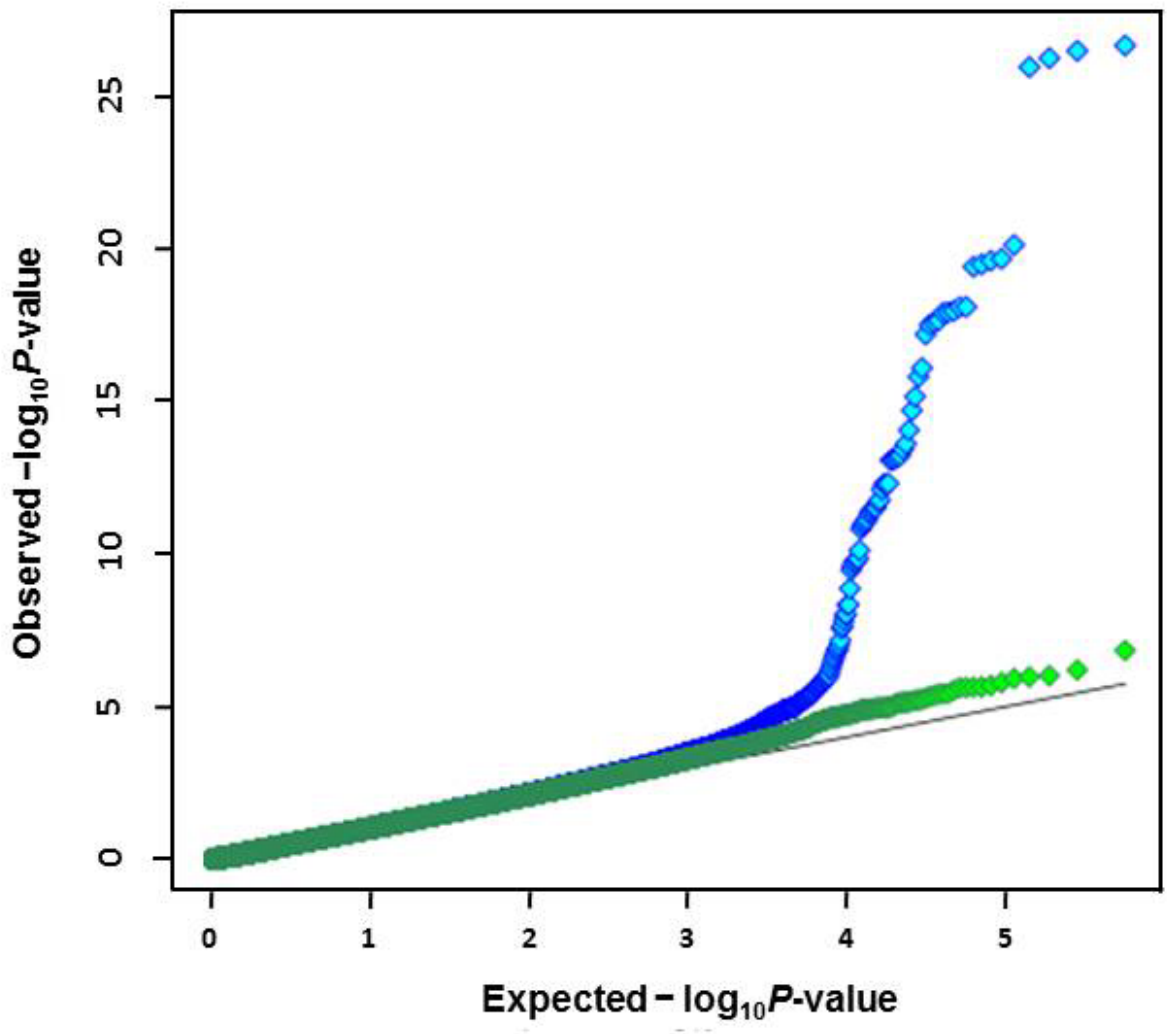


Supplementary Figure S1 Classification of gout.

Gout can be pathophysiologically classified into the 'renal overload' (ROL) type, the 'renal underexcretion' (RUE) type, or the combined type, based on the clinical parameters, UUE and FE_{UA}. The unit of UUE is 'mg/hr/1.73m^2.' Urate is an end-product of purine metabolism, and excreted from kidney (renal excretion pathway) or from extra-renal tissues (extra-renal excretion pathway). Therefore, elevated SUA with high UUE (>25 mg/hr/1.73m^2) is caused by renal urate overload (overproduction and/or extra-renal underexcretion of urate), while increased SUA with low FE_{UA} (<5.5%) results from renal urate underexcretion. SUA, serum uric acid. UUE, urinary urate excretion. FE_{UA}, fractional excretion of urate clearance.

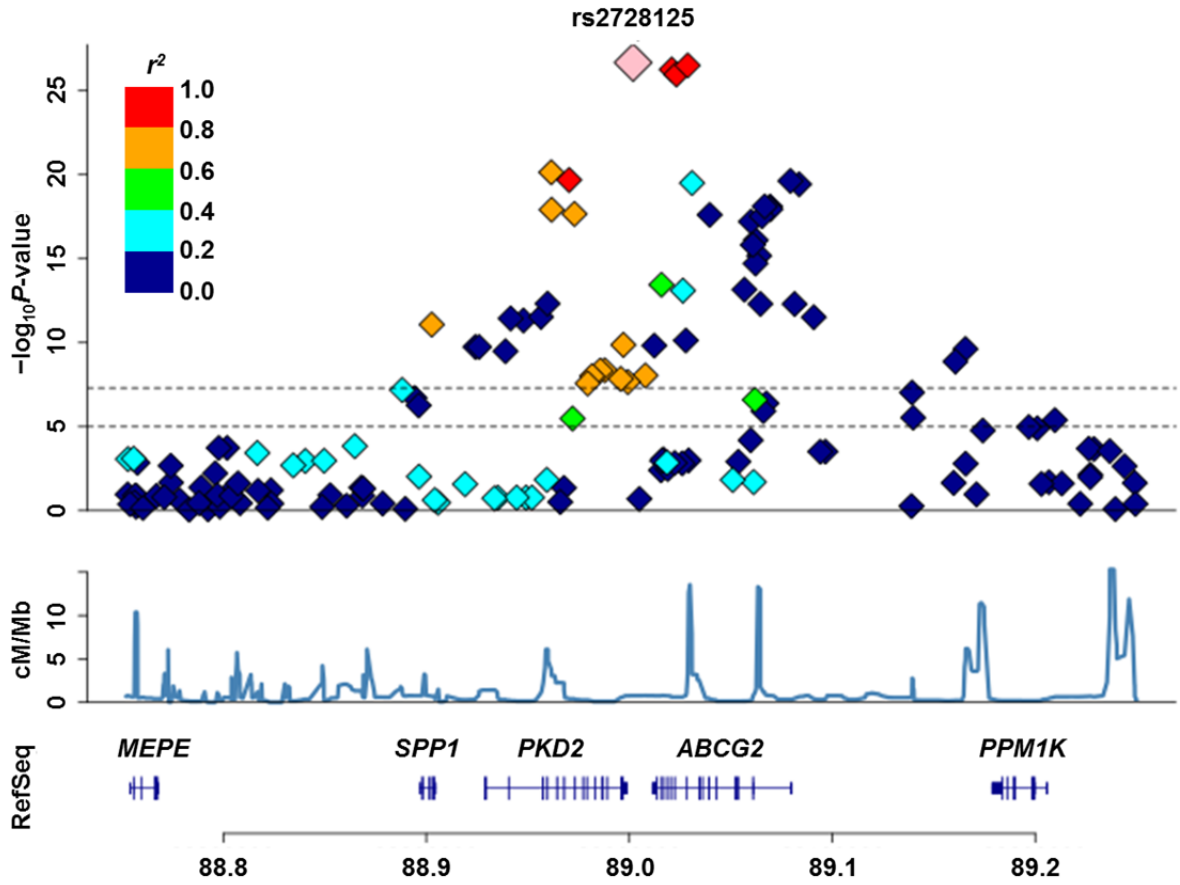


Supplementary Figure S2 Result of principal component analysis including case and control samples used in this GWAS and four HapMap populations. JPT, Japanese in Tokyo, Japan. CEU, CEPH (Utah residents with ancestry from northern and western Europe). YRI, Yoruba in Ibadan, Nigeria. CHB, Han Chinese in Beijing, China.

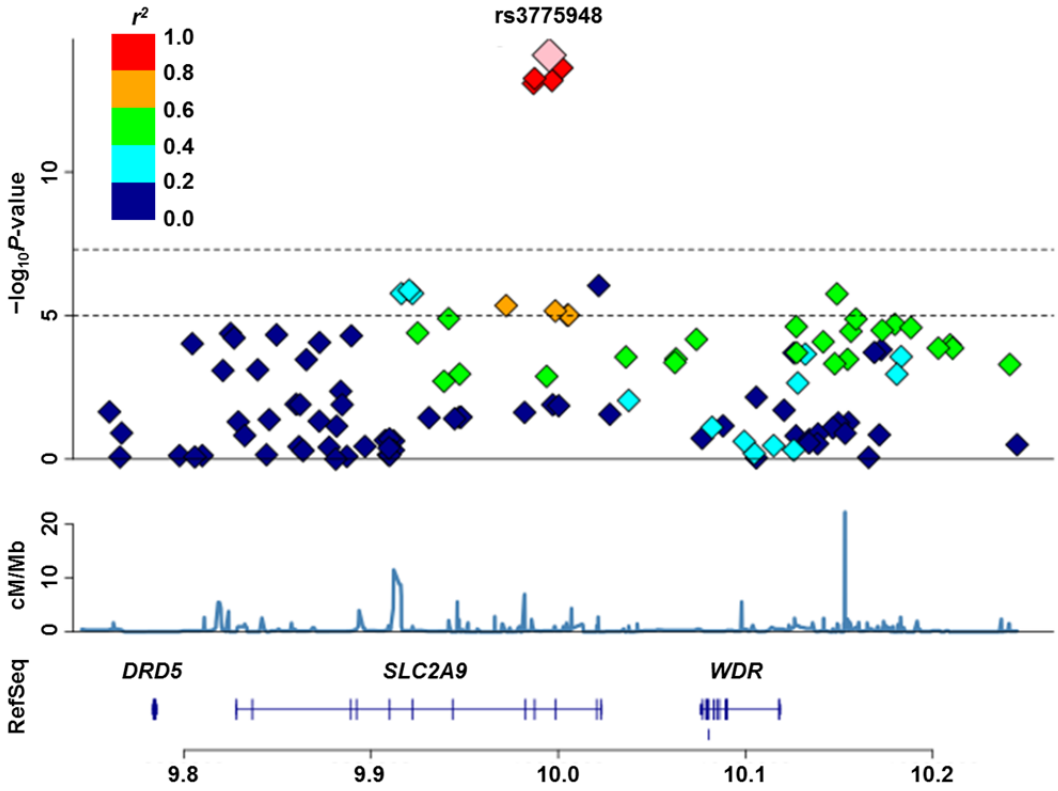


Supplementary Figure S3　Quantile-Quantile plot of p value distribution for association.

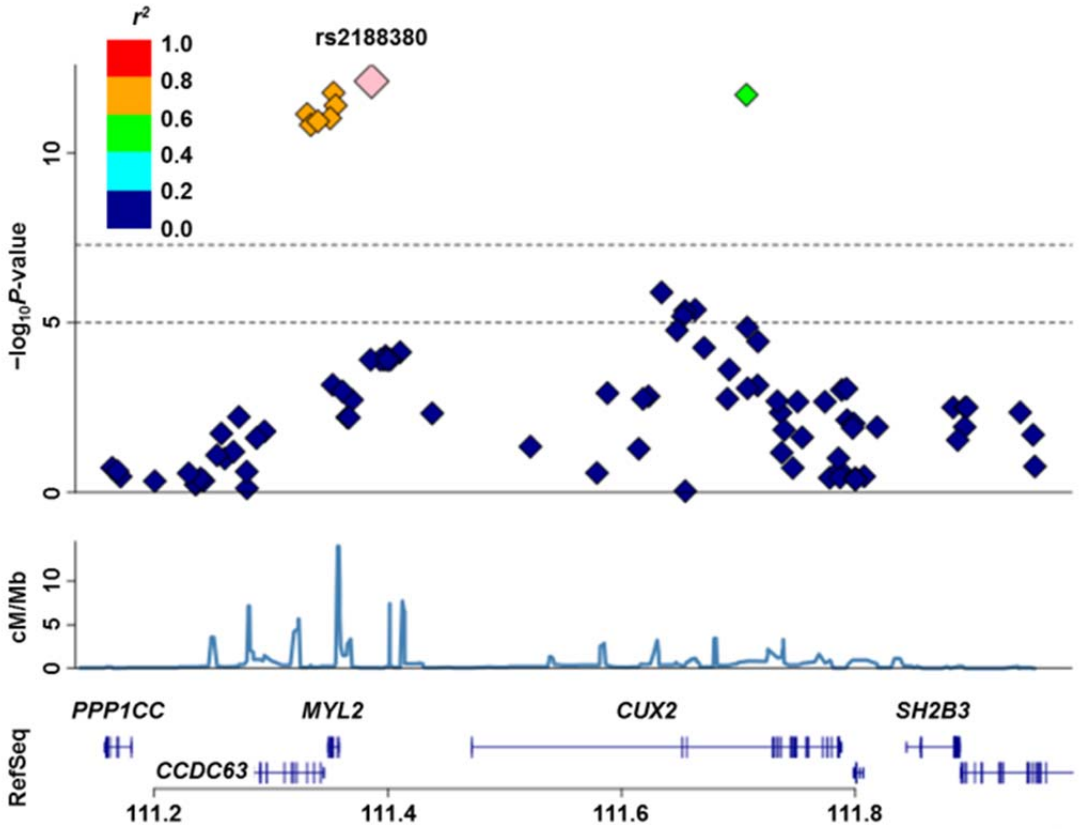
Results for all SNPs tested are plotted in blue. Results excluding SNPs within 500 kb from the SNPs strongly associated at $p < 5.0 \times 10^{-8}$ (rs2728125 of *ABCG2*, rs3775948 of *SLC2A9*, and rs2188380 of *MYL2-CUX2*) are plotted in green.



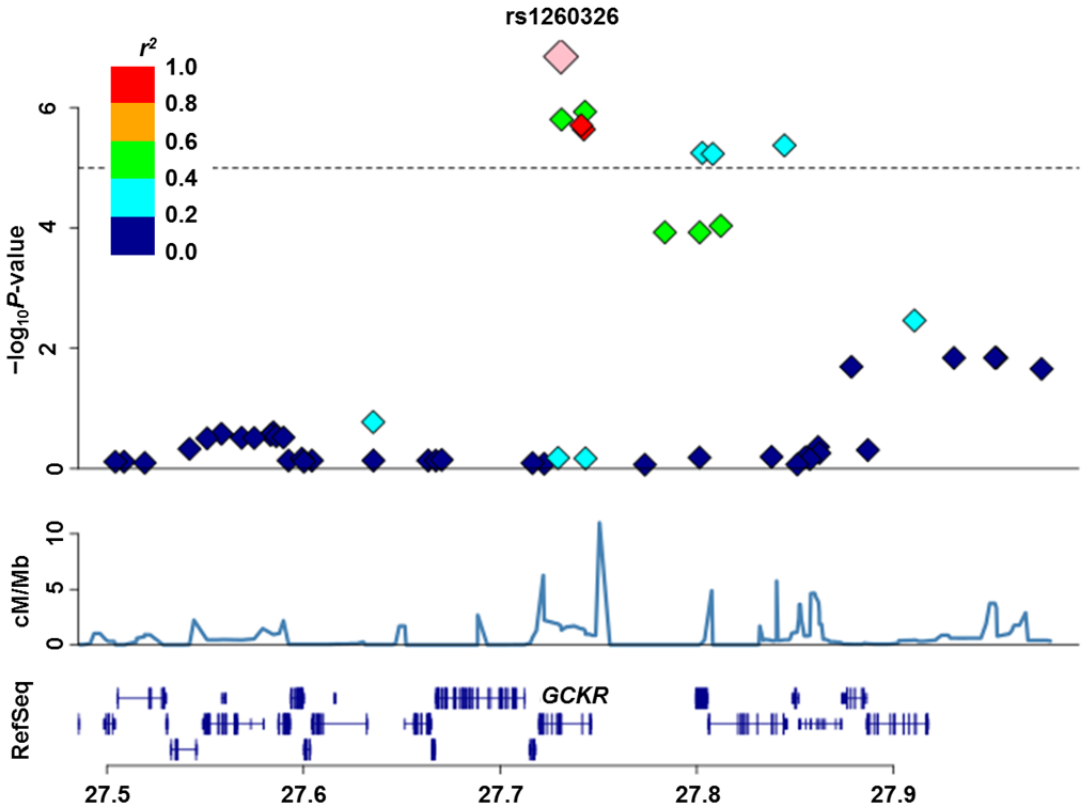
Supplementary Figure S4A Regional association plots for six discovered loci (Larger version of Figure 2A; *ABCG2* locus).



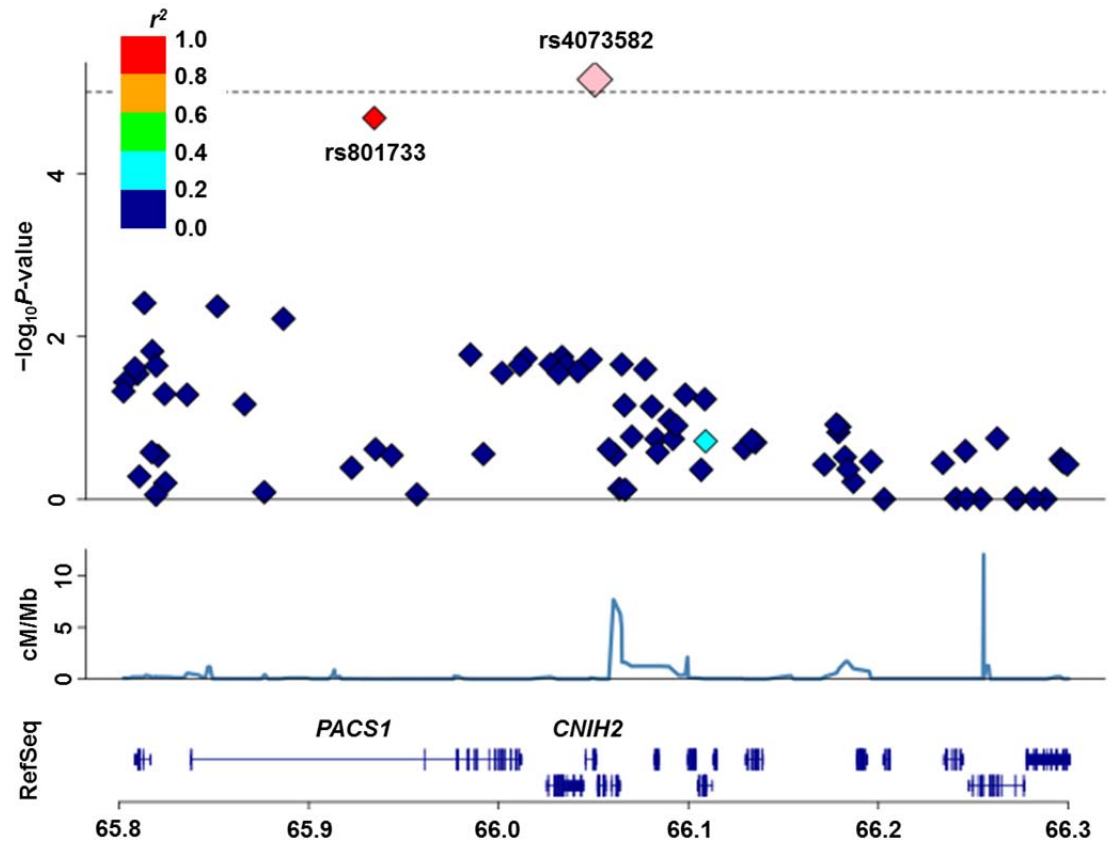
Supplementary Figure S4B Regional association plots for six discovered loci (Larger version of Figure 2B; *SCL2A9* locus).



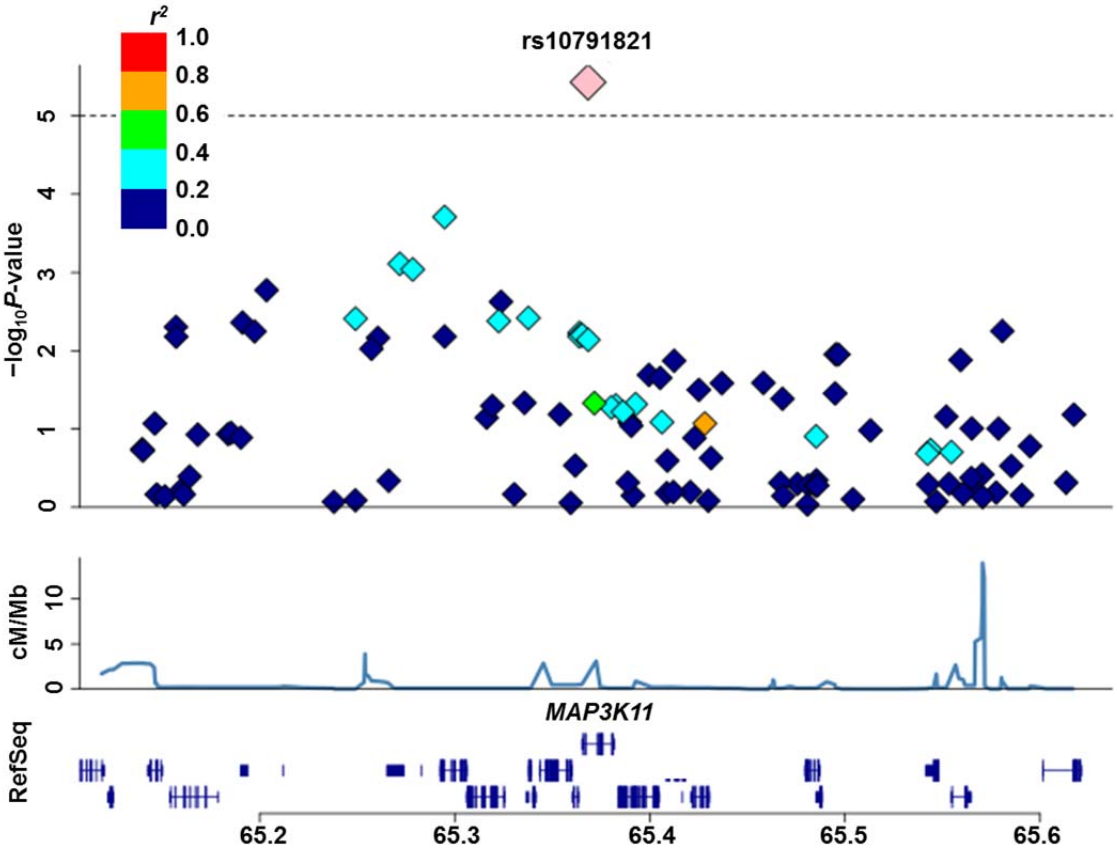
Supplementary Figure S4C Regional association plots for six discovered loci (Larger version of Figure 2C; *MYL2-CUX2* locus).



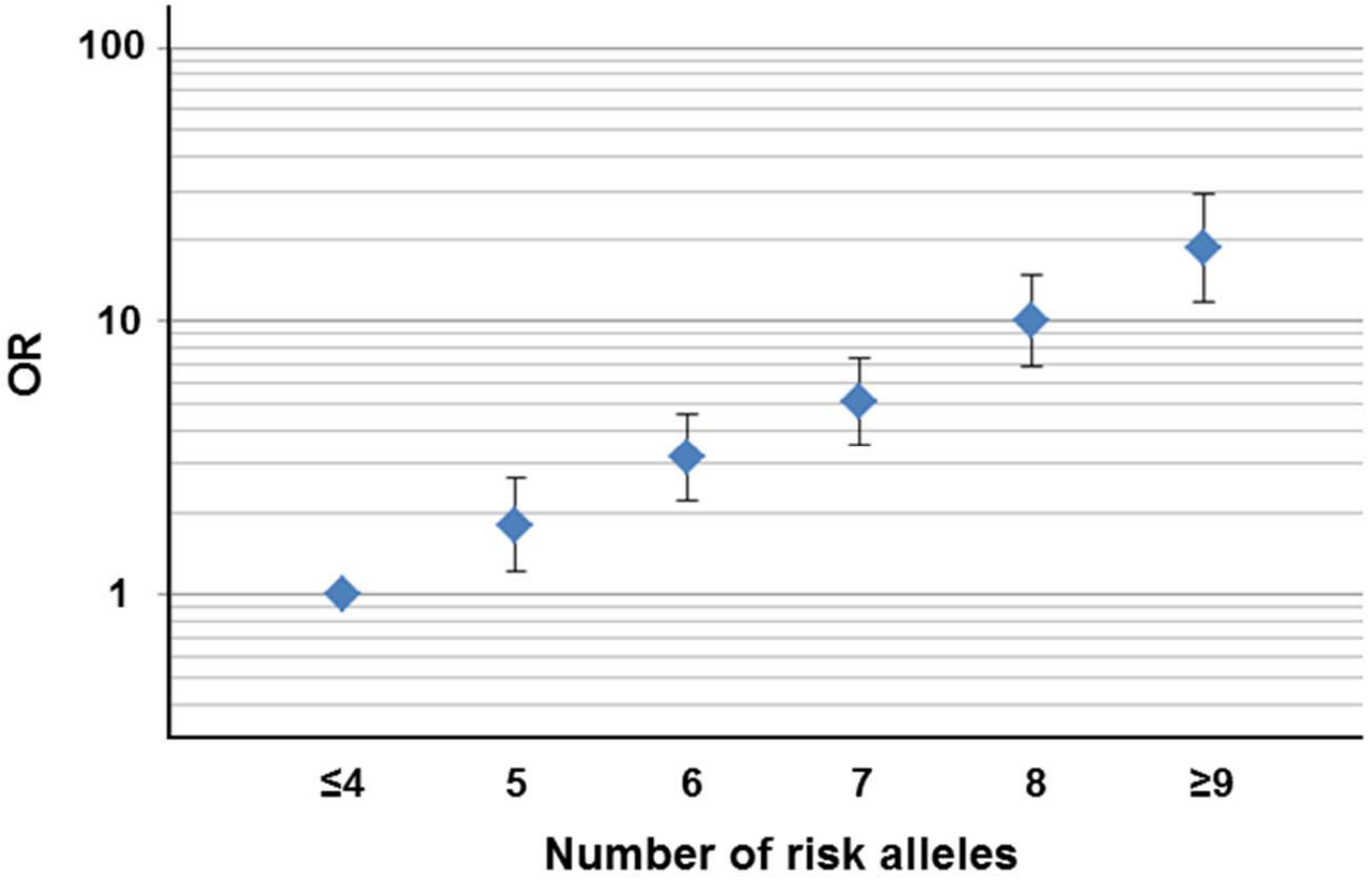
Supplementary Figure S4D Regional association plots for six discovered loci (Larger version of Figure 2D; *GCKR* locus).



Supplementary Figure S4E Regional association plots for six discovered loci (Larger version of Figure 2E; *CNIH-2* locus).

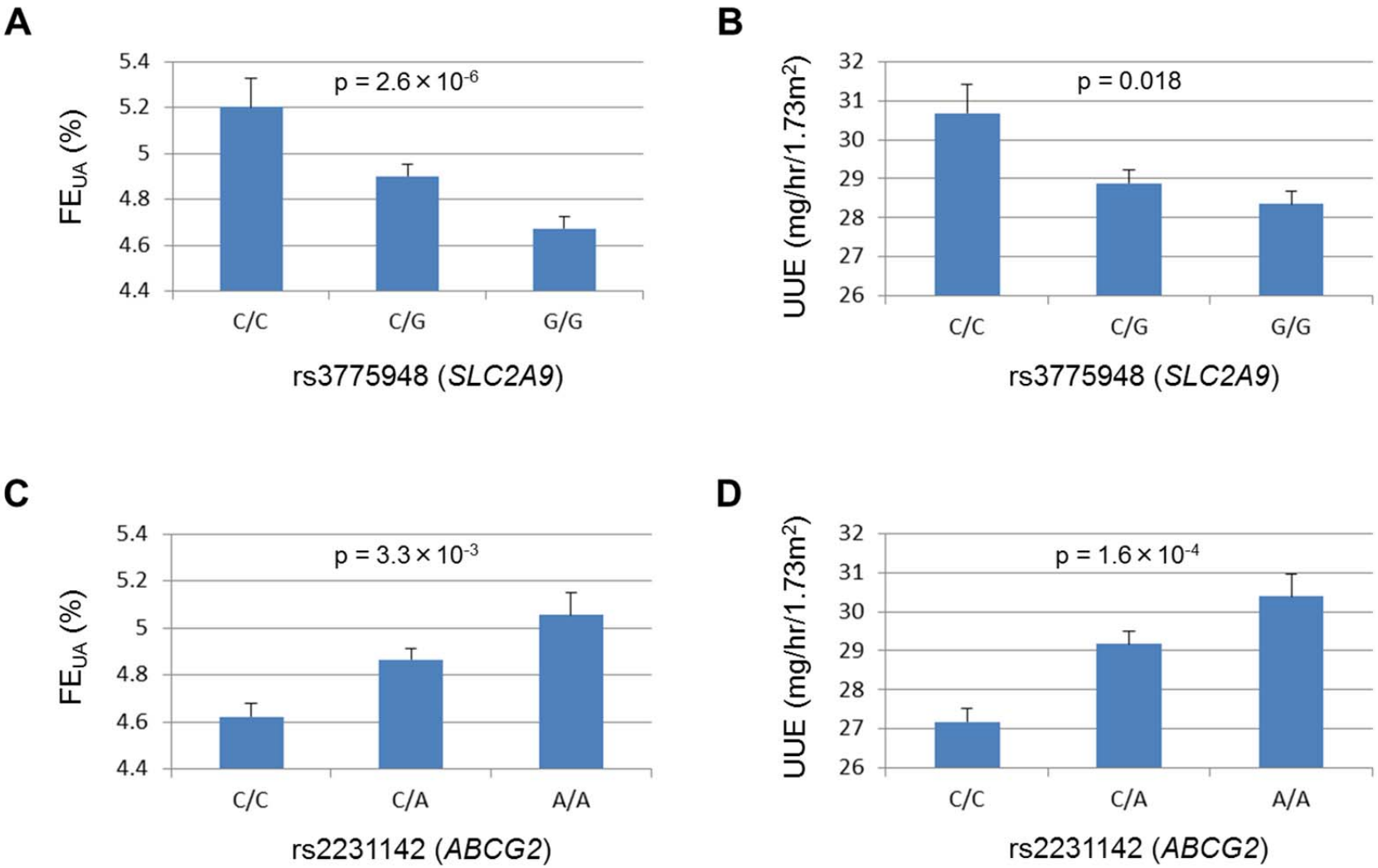


Supplementary Figure S4F Regional association plots for six discovered loci (Larger version of Figure 2F; *MAP3K11* locus).



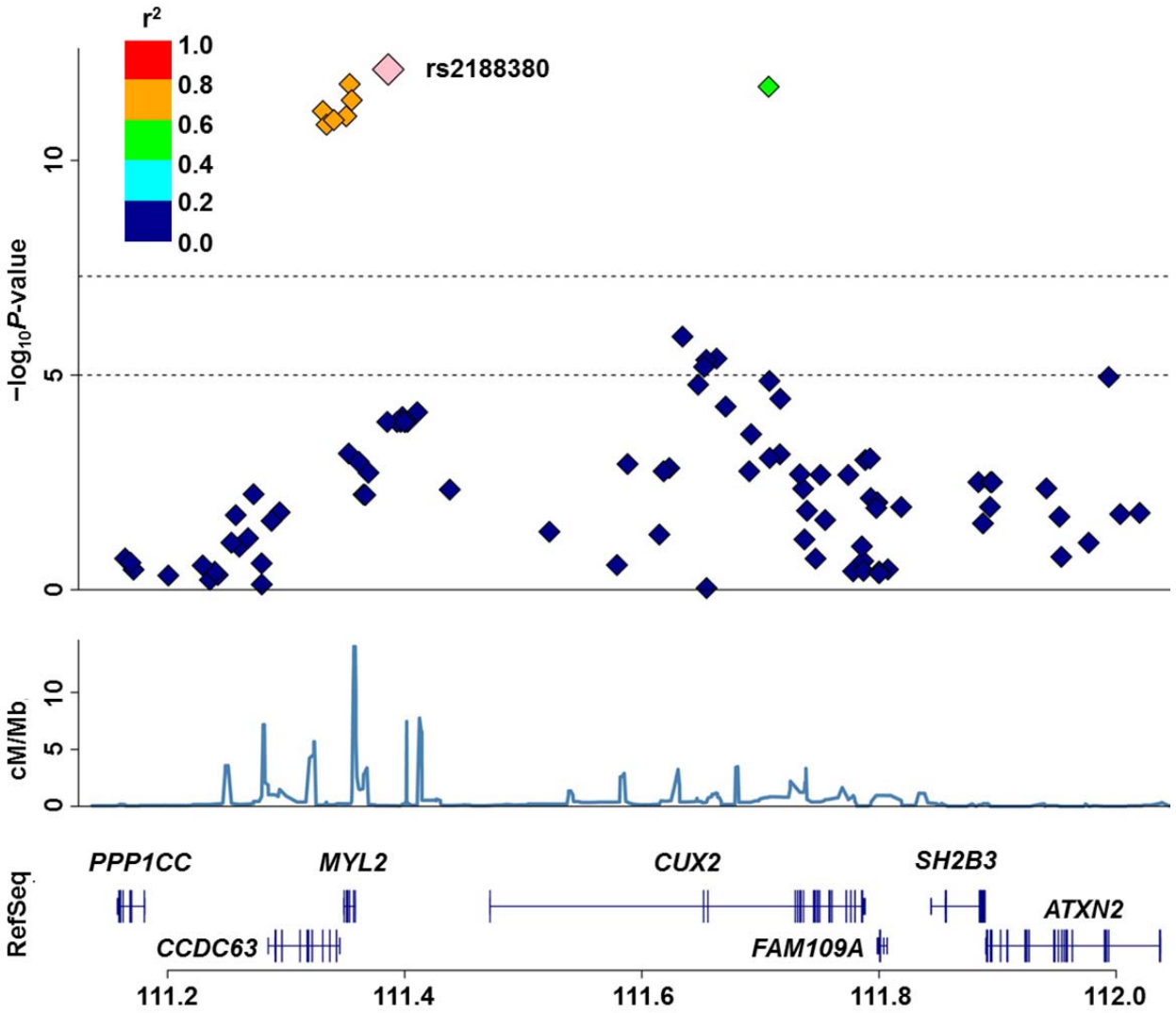
Supplementary Figure S5　Cumulative effect of six gout-associated SNPs for developing gout.

A genetic risk score was defined as the number of risk alleles over the following six SNPs: four SNPs identified by the present study (rs3775948 of *SLC2A9*, rs2188380 of *MYL2-CUX2*, rs1260326 [Leu446Pro] of *GCKR*, and rs4073582 of *CNIH-2*) and two nonsynonymous SNPs (rs72552713 [Gln126Ter] and rs2231142 [Gln141Lys] of *ABCG2*), which have been established as strong gout risk SNPs.



Supplementary Figure S6　Relationship between clinical parameters (FE_{UA} and UUE) and the SNPs of *SLC2A9* and *ABCG2*.

FE_{UA} and UUE significantly decreased as the risk allele of *SLC2A9* (rs3775948) increased (A, B), whereas they increased as the risk allele of *ABCG2* (rs2231142) increased (C, D). Because RUE type and ROL type are defined by FE_{UA} and UUE (Supplementary Figure S1), these are consistent with the results shown in Supplementary Table S9. All bars show mean ± SEM.



Supplementary Figure S7　Extended regional association plot of *MYL2-CUX2* locus.

Near rs2188380 of *MYL2-CUX2*, there is rs653178 of *ATXN2*, which was previously reported in European ancestry to have an association with SUA, although rs653178 is monomorphic in a Japanese population. Conversely, rs2188380 identified in the present study with Japanese is monomorphic in European and African populations.

Supplementary Table S1 Clinical characteristics of case and control

	GWAS stage		Replication stage	
	Case	Control	Case	Control
Number	945	1213	1048	1334
Age (year)	46.5 ± 11.2	65.8 ± 8.4	44.9 ± 11.4	52.4 ± 8.6
Body-mass index (kg/m^2)	25.1 ± 3.6	21.8 ± 3.3	25.0 ± 3.5	23.2 ± 2.7
Serum uric acid (mg/dl)	8.5 ± 1.2	5.5 ± 1.1	8.6 ± 1.3	5.6 ± 0.9

Plus-minus values are means ± SD

Supplementary Table S2 Clinical parameters for each specific type of gout patient

	Number (%)	SUA	FE_{UA}	UUE
ROL type	375 (23.2%)	8.18 ± 1.10	6.73 ± 1.25	35.8 ± 8.3
RUE type	509 (31.6%)	8.38 ± 1.16	3.84 ± 0.79	20.5 ± 3.5
Combined type	664 (41.2%)	8.83 ± 1.25	4.40 ± 0.70	31.8 ± 6.9
Normal type	65 (4.0%)	7.72 ± 1.12	6.46 ± 0.90	21.2 ± 3.5
All	1613 (100%)	8.49 ± 1.22	4.85 ± 1.46	28.7 ± 8.9

Plus-minus values are means ± SD

SUA, serum uric acid; FE_{UA}, fractional excretion of urate clearance; UUE, urinary urate excretion; ROL, renal overload; RUE, renal underexcretion.

Among 1993 clinically-defined cases, 1613 patients had information such as clinical parameters (UUE and FE_{UA}) to classify their clinical subtypes.

Supplementary Table S3 Concomitant diseases of gout patients

Number (%)	Hypertension	Dyslipidemia	Diabetes mellitus	Ischemic heart disease	Stroke	Renal impairment*
GWAS stage	249 (26.3%)	42 (4.4%)	37 (3.9%)	19 (2.0%)	9 (0.95%)	11 (1.2%)
Replication stage	317 (30.2%)	58 (5.5%)	42 (4.0%)	26 (2.5%)	9 (0.86%)	4 (0.38%)
All	566 (28.4%)	100 (5.0%)	79 (4.0%)	45 (2.3%)	18 (0.90%)	15 (0.75%)

*Renal impairment is defined with high serum creatinine (≥1.5 mg/dl).

Supplementary Table S4 Summary of GWAS and replication study of 16 SNPs

					GWAS[§]				Replication study[‖]				Meta-analysis[††]		Heterogeneity	
					Freq.				Freq.							
SNP*	Chr.	Position (bp)[†]	Gene	A1/A2[‡]	Cases	Controls	OR (95% CI)	p Value	Cases	Controls	OR (95% CI)	p Value[‡‡]	OR (95% CI)	p Value[g]	Cochran's Q	I^2 (%)
rs1260326**	2	27730940	*GCKR*	T/C	0.62	0.54	1.39 (1.23-1.57)	1.2×10^{-7}	0.61	0.55	1.32 (1.18-1.49)	**2.8×10^{-6}**	1.36 (1.25-1.48)	**1.9×10^{-12}**	0.57	0
rs16835687	3	124327247	*KALRN*	G/A	0.17	0.12	1.48 (1.24-1.75)	7.8×10^{-6}	0.15	0.12	1.22 (1.03-1.45)	0.019	1.34 (1.12-1.62)	1.9×10^{-3}	0.12	58.2
rs4637240	3	127150025	*PLXNA1-TPRA1*	C/T	0.87	0.81	1.5 (1.27-1.77)	1.8×10^{-6}	0.84	0.83	1.08 (0.92-1.26)	0.35	1.27 (0.92-1.76)	0.15	4.3×10^{-3}	87.7
rs3775948**	4	9995182	*SLC2A9*	G/C	0.68	0.56	1.64 (1.45-1.86)	6.7×10^{-15}	0.67	0.56	1.57 (1.40-1.77)	**7.6×10^{-14}**	1.61 (1.47-1.75)	**5.5×10^{-27}**	0.63	0
rs2728125**	4	89001893	*ABCG2*	C/T	0.40	0.25	2.05 (1.80-2.34)	1.5×10^{-27}	0.40	0.24	2.03 (1.79-2.30)	**8.3×10^{-29}**	2.04 (1.86-2.23)	**7.2×10^{-54}**	0.90	0
rs6916538	6	100618009	*MCHR2-SIM1*	A/G	0.51	0.44	1.34 (1.19-1.51)	2.0×10^{-6}	0.48	0.46	1.09 (0.97-1.23)	0.13	1.21 (0.99-1.48)	0.062	1.7×10^{-2}	82.4
rs731305	7	157682840	*PTPRN2*	C/T	0.63	0.56	1.36 (1.20-1.54)	8.9×10^{-7}	0.61	0.61	1.02 (0.91-1.15)	0.70	1.18 (0.89-1.56)	0.25	1.1×10^{-3}	90.7
rs7007064	8	63099432	*ASPH-NKAIN3*	A/C	0.76	0.70	1.38 (1.21-1.59)	3.2×10^{-6}	0.73	0.75	0.90 (0.79-1.03)	0.12	1.12 (0.73-1.70)	0.61	8.8×10^{-6}	94.9
rs10791821***	11	65368323	*MAP3K11*	G/A	0.94	0.90	1.75 (1.38-2.22)	2.8×10^{-6}	0.94	0.92	1.41 (1.12-1.77)	3.4×10^{-3}	1.57 (1.33-1.85)	1.0×10^{-7}	0.19	41.2
rs4073582**	11	66050712	*CNIH-2*	G/A	0.95	0.91	1.78 (1.39-2.29)	5.3×10^{-6}	0.94	0.91	1.55 (1.23-1.96)	**1.6×10^{-4}**	1.66 (1.40-1.96)	**6.4×10^{-9}**	0.43	0
rs11216561	11	117685575	*FXYD2-DSCAML1*	C/T	0.11	0.07	1.70 (1.38-2.10)	7.2×10^{-7}	0.10	0.08	1.33 (1.09-1.63)	5.7×10^{-3}	1.50 (1.18-1.91)	1.0×10^{-3}	0.098	63.4
rs2188380**	12	111386127	*MYL2-CUX2*	T/C	0.85	0.76	1.78 (1.52-2.08)	5.7×10^{-13}	0.86	0.78	1.73 (1.48-2.02)	**2.0×10^{-12}**	1.75 (1.57-1.96)	**1.6×10^{-23}**	0.81	0
rs9806234	15	74663033	*CYP11A1-SEMA7A*	G/A	0.62	0.55	1.34 (1.18-1.51)	3.1×10^{-6}	0.58	0.58	1.02 (0.91-1.15)	0.70	1.17 (0.90-1.52)	0.24	1.9×10^{-3}	89.7
rs931794	15	78826180	*AGPHD1*	A/G	0.67	0.60	1.33 (1.18-1.51)	6.5×10^{-6}	0.64	0.64	1.00 (0.89-1.13)	0.97	1.16 (0.87-1.53)	0.31	1.3×10^{-3}	90.4
rs13755	17	37223458	*PLXDC1*	A/G	0.17	0.13	1.47 (1.24-1.73)	8.3×10^{-6}	0.14	0.16	0.87 (0.74-1.02)	0.088	1.13 (0.67-1.88)	0.65	1.2×10^{-5}	94.8
rs242676	18	58754937	*MC4R-CDH20*	A/G	0.72	0.65	1.36 (1.19-1.55)	3.9×10^{-6}	0.70	0.69	1.01 (0.89-1.14)	0.88	1.17 (0.88-1.57)	0.29	1.3×10^{-3}	90.4

Chr., chromosome; Freq., frequency of A1; OR, odds ratio; CI, confidence interval.

*dbSNP rs number. SNPs at genome-wide significance levels are marked with "**" and a suggestive SNP is marked with "***"

[†]SNP positions are based on NCBI human genome reference sequence Build 37.4.

[‡]A1 is a risk-associated allele and A2 is a non-risk-associated allele.

[§]945 gout cases and 1213 controls.

[‖]1048 gout cases and 1334 controls.

[††]The inverse-variance fixed-effects model meta-analysis was used for estimating summary OR. If heterogeneity was present by the statistical test ($p_{het} < 0.05$) or measure ($I^2 > 50\%$), we performed DerSimonian and Laird random-effects model meta-analysis.

[‡‡]p values smaller than 3.1×10^{-3} (adjusting for 16 tests with Bonferroni correction) in replication study are shown in bold letters. p values smaller than 5.0×10^{-8} in meta-analyses are shown in bold letters.

Supplementary Table S5 Power of the present study design

	Minor allele frequency of control		
Odds ratio	0.2	0.3	0.4
2.0	99.5%	100.0%	100.0%
1.8	92.7%	98.2%	99.0%
1.6	57.1%	76.9%	83.0%
1.4	8.7%	18.6%	24.5%

The significance thresholds are calculated to be $\alpha = 1.0 \times 10^{-5}$ and 3.1×10^{-3} (= 0.05/16) for GWAS and replication stages, respectively.

Supplementary Table S6A Imputation analysis near *MYL2-CUX2* locus

SNP*	Chr.	Position (bp)†	Gene	p Value	r²‡
rs12227162	12	111367244	*MYL2-CUX2*	4.4×10^{-14}	0.92
rs149607519	12	111389437	*MYL2-CUX2*	6.3×10^{-14}	0.99
rs17550549	12	111357471	*MYL2*	6.4×10^{-14}	0.61
rs10849917	12	111357074	*MYL2*	6.8×10^{-14}	0.60
rs2188380	12	111386127	*MYL2-CUX2*	7.2×10^{-14}	-
rs7488411	12	111356598	*MYL2*	7.2×10^{-14}	0.60
rs12311834	12	111354700	*MYL2*	7.7×10^{-14}	0.56
rs10849916	12	111355206	*MYL2*	7.7×10^{-14}	0.58
rs3782888	12	111355606	*MYL2*	8.3×10^{-14}	0.60
rs117607209	12	111354703	*MYL2*	8.9×10^{-14}	0.59
rs61943010	12	111354623	*MYL2*	1.1×10^{-13}	0.60
rs11065773	12	111355100	*MYL2*	1.1×10^{-13}	0.60
rs61943000	12	111354106	*MYL2*	1.3×10^{-13}	0.60
rs61942999	12	111353762	*MYL2*	1.3×10^{-13}	0.60
rs2301610	12	111353556	*MYL2*	1.3×10^{-13}	0.60
rs11065747	12	111326666	*CCDC63*	1.3×10^{-13}	0.56
rs2078847	12	111352478	*MYL2*	1.3×10^{-13}	0.60
rs11065770	12	111351937	*MYL2*	1.3×10^{-13}	0.60
rs916164	12	111351599	*MYL2*	1.4×10^{-13}	0.60
rs11065769	12	111351439	*MYL2*	1.4×10^{-13}	0.60
rs2071629	12	111351186	*MYL2*	1.4×10^{-13}	0.60
rs3858704	12	111705893	*CUX2*	3.9×10^{-13}	0.50
rs4766566	12	111706877	*CUX2*	4.0×10^{-13}	0.50
rs11065746	12	111326655	*CCDC63*	5.1×10^{-13}	0.60
rs3825389	12	111350771	*MYL2*	5.4×10^{-13}	0.60
rs3782889	12	111350655	*MYL2*	5.5×10^{-13}	0.60
rs3782890	12	111350531	*MYL2*	5.5×10^{-13}	0.60
rs3782891	12	111350457	*MYL2*	5.6×10^{-13}	0.60
rs11065766	12	111349849	*MYL2*	5.6×10^{-13}	0.60
rs12231049	12	111349223	*MYL2*	5.8×10^{-13}	0.60
rs117139109	12	111346382	*CCDC63*	5.9×10^{-13}	0.59
rs11065750	12	111331016	*CCDC63*	7.2×10^{-13}	0.60
rs11065749	12	111329227	*CCDC63*	7.2×10^{-13}	0.60
rs10774609	12	111325265	*CCDC63*	9.3×10^{-13}	0.59
rs11065751	12	111331156	*CCDC63*	1.0×10^{-12}	0.60
rs10849914	12	111325437	*CCDC63*	1.4×10^{-12}	0.59
rs78900292	12	111341921	*CCDC63*	1.5×10^{-12}	0.59

rs117528052	12	111341920	*CCDC63*	1.5×10^{-12}	0.59
rs11065752	12	111331165	*CCDC63*	1.6×10^{-12}	0.60
rs11065753	12	111331685	*CCDC63*	1.6×10^{-12}	0.60
rs7312231	12	111333224	*CCDC63*	1.6×10^{-12}	0.60
rs10849915	12	111333622	*CCDC63*	1.6×10^{-12}	0.60
rs1858881	12	111334117	*CCDC63*	1.7×10^{-12}	0.60
rs6489821	12	111334318	*CCDC63*	1.7×10^{-12}	0.60
rs2339598	12	111341925	*CCDC63*	1.8×10^{-12}	0.58
rs11065758	12	111341026	*CCDC63*	1.8×10^{-12}	0.58
rs6489822	12	111334375	*CCDC63*	1.8×10^{-12}	0.60
rs35856328	12	111335360	*CCDC63*	1.8×10^{-12}	0.60
rs11065764	12	111343443	*CCDC63*	1.8×10^{-12}	0.60
rs11065763	12	111343000	*CCDC63*	1.9×10^{-12}	0.60
rs11065762	12	111342722	*CCDC63*	1.9×10^{-12}	0.60
rs2283353	12	111342017	*CCDC63*	1.9×10^{-12}	0.60
rs146280669	12	111335756	*CCDC63*	2.0×10^{-12}	0.60
rs7303257	12	111324923	*CCDC63*	2.1×10^{-12}	0.60
rs11610779	12	111336560	*CCDC63*	2.2×10^{-12}	0.60
rs7305904	12	111337891	*CCDC63*	2.3×10^{-12}	0.60
rs11065756	12	111338794	*CCDC63*	2.4×10^{-12}	0.60
rs11065757	12	111340788	*CCDC63*	2.4×10^{-12}	0.60
rs10774610	12	111340243	*CCDC63*	2.5×10^{-12}	0.60
rs2339717	12	111696528	*CUX2*	2.9×10^{-12}	0.48
rs6490029	12	111698457	*CUX2*	3.1×10^{-12}	0.48
rs916682	12	111699146	*CUX2*	5.1×10^{-12}	0.49
rs11065836	12	111671076	*CUX2*	4.4×10^{-9}	0.23
rs2106410	12	111631946	*CUX2*	1.4×10^{-7}	0.19
rs4766552	12	111631765	*CUX2*	1.4×10^{-7}	0.25
rs4766553	12	111634281	*CUX2*	5.5×10^{-7}	0.19
rs56119815	12	111665521	*CUX2*	1.4×10^{-6}	0.14
rs3809286	12	111664404	*CUX2*	1.7×10^{-6}	0.11
rs4766558	12	111664061	*CUX2*	1.9×10^{-6}	0.11
rs7969686	12	111665388	*CUX2*	2.4×10^{-6}	0.11
rs7962233	12	111655513	*CUX2*	2.7×10^{-6}	0.14
rs10774615	12	111659096	*CUX2*	2.8×10^{-6}	0.11
rs4766556	12	111659074	*CUX2*	2.9×10^{-6}	0.11
rs3825398	12	111651949	*CUX2*	2.9×10^{-6}	0.12
rs10083213	12	111654363	*CUX2*	2.9×10^{-6}	0.11
rs11065832	12	111662984	*CUX2*	3.5×10^{-6}	0.11

rs10082818	12	111663177	*CUX2*	3.5×10^{-6}	0.11
rs7971185	12	111660599	*CUX2*	3.8×10^{-6}	0.13
rs2339715	12	111657745	*CUX2*	4.2×10^{-6}	0.13
rs4766559	12	111666984	*CUX2*	4.6×10^{-6}	0.15
rs3809288	12	111652522	*CUX2*	4.8×10^{-6}	0.11
rs10744769	12	111650780	*CUX2*	5.5×10^{-6}	0.11
rs2339716	12	111680885	*CUX2*	6.5×10^{-6}	0.12
rs3925618	12	111649686	*CUX2*	7.0×10^{-6}	0.14
rs1034603	12	111649344	*CUX2*	7.3×10^{-6}	0.14
rs1034602	12	111649179	*CUX2*	7.4×10^{-6}	0.14
rs4766557	12	111664044	*CUX2*	8.4×10^{-6}	0.12
rs10774614	12	111650339	*CUX2*	8.5×10^{-6}	0.13
rs6490037	12	111713671	*CUX2*	9.9×10^{-6}	0.17

Chr., chromosome.

*dbSNP rs number.

†SNP positions are based on NCBI human genome reference sequence Build 37.4.

‡r^2 indicates the pairwise linkage disequilibrium with rs2188380.

Supplementary Table S6B Imputation analysis near *GCKR* locus

SNP*	Chr.	Position (bp)†	Gene	p Value	r^{2}‡
rs1260326	2	27730940	*GCKR*	1.7×10^{-7}	-
rs814295	2	27743215	*GCKR*	1.1×10^{-6}	0.48
rs6744393	2	27750139	*GCKR*	1.1×10^{-6}	0.48
rs74928908	2	27744089	*GCKR*	1.2×10^{-6}	0.47
rs780092	2	27743154	*GCKR*	1.2×10^{-6}	0.47
rs78680773	2	27751562	*GCKR*	1.2×10^{-6}	0.45
rs3817588	2	27731212	*GCKR*	1.4×10^{-6}	0.50
rs780093	2	27742603	*GCKR*	2.1×10^{-6}	0.88
rs1313566	2	27748904	*GCKR*	2.3×10^{-6}	0.88
rs182700961	2	27781772	*GCKR-C2orf16*	3.2×10^{-6}	0.22
rs780094	2	27741237	*GCKR*	3.2×10^{-6}	0.92
rs6547692	2	27734972	*GCKR*	3.5×10^{-6}	0.93
rs62131879	2	27755112	*GCKR*	3.5×10^{-6}	0.23
rs10181342	2	27757343	*GCKR*	3.6×10^{-6}	0.23
rs116443177	2	27764122	*GCKR*	3.6×10^{-6}	0.23
rs62131881	2	27764781	*GCKR*	3.7×10^{-6}	0.23
rs62131882	2	27765480	*GCKR*	3.7×10^{-6}	0.23
rs62141278	2	27768381	*GCKR*	3.8×10^{-6}	0.23
rs780096	2	27741072	*GCKR*	3.8×10^{-6}	0.92

rs780095	2	27741105	*GCKR*	3.8×10^{-6}	0.92
rs62141279	2	27771415	*GCKR-C2orf16*	3.9×10^{-6}	0.24
rs62141281	2	27777651	*GCKR-C2orf16*	4.1×10^{-6}	0.23
rs2384627	2	27774449	*GCKR-C2orf16*	4.2×10^{-6}	0.23
rs6751087	2	27778016	*GCKR-C2orf16*	4.2×10^{-6}	0.23
rs1881396	2	27844601	*ZNF512*	4.8×10^{-6}	0.24
rs13405762	2	27834615	*ZNF512*	5.3×10^{-6}	0.23
rs78170284	2	27835082	*ZNF512*	5.4×10^{-6}	0.23
rs1881395	2	27838549	*ZNF512*	5.4×10^{-6}	0.23
rs7571558	2	27839832	*ZNF512*	5.4×10^{-6}	0.23
rs62138971	2	27840754	*ZNF512*	5.4×10^{-6}	0.23
rs6547735	2	27831607	*ZNF512*	5.7×10^{-6}	0.23
rs6719960	2	27830067	*ZNF512*	5.7×10^{-6}	0.23
rs2141372	2	27827196	*ZNF512*	5.7×10^{-6}	0.23
rs62138968	2	27824485	*ZNF512*	5.7×10^{-6}	0.23
rs56725354	2	27824168	*ZNF512*	5.7×10^{-6}	0.23
rs1919129	2	27818721	*ZNF512*	5.8×10^{-6}	0.23
rs62138966	2	27819172	*ZNF512*	5.8×10^{-6}	0.23
rs62138965	2	27816593	*ZNF512*	5.8×10^{-6}	0.23
rs76013440	2	27816315	*ZNF512*	5.8×10^{-6}	0.23
rs1881397	2	27832285	*ZNF512*	5.9×10^{-6}	0.23
rs60854669	2	27786929	*GCKR-C2orf16*	6.1×10^{-6}	0.23
rs965813	2	27789861	*GCKR-C2orf16*	6.2×10^{-6}	0.23
rs59876138	2	27792323	*GCKR-C2orf16*	6.2×10^{-6}	0.23
rs6704596	2	27796927	*GCKR-C2orf16*	6.3×10^{-6}	0.23
rs62138964	2	27814438	*ZNF512*	6.3×10^{-6}	0.23
rs62138963	2	27814374	*ZNF512*	6.3×10^{-6}	0.23
rs3811644	2	27802805	*C2orf16*	6.3×10^{-6}	0.23
rs6734059	2	27808154	*ZNF512*	6.5×10^{-6}	0.23
rs62141291	2	27784034	*GCKR-C2orf16*	6.6×10^{-6}	0.23
rs62141292	2	27784300	*GCKR-C2orf16*	6.6×10^{-6}	0.23
rs62141290	2	27783392	*GCKR-C2orf16*	9.2×10^{-6}	0.22

Chr., chromosome.

*dbSNP rs number.

†SNP positions are based on NCBI human genome reference sequence Build 37.4.

‡r^2 indicates the pairwise linkage disequilibrium with rs1260326.

Supplementary Table S6C Imputation analysis near *CNIH-2* locus

SNP*	Chr.	Position (bp)†	Gene	p Value	$r^{2‡}$
rs524859	11	66041079	*RAB1B*	3.9×10^{-6}	1.00
rs4073582	11	66050712	*CNIH-2*	4.8×10^{-6}	-
rs801742	11	65914766	*PACS1*	6.9×10^{-6}	0.96

Chr., chromosome.

*dbSNP rs number.

†SNP positions are based on NCBI human genome reference sequence Build 37.4.

‡r^2 indicates the pairwise linkage disequilibrium with rs4073582.

Supplementary Table S6D Imputation analysis near *MAP3K11* locus

SNP*	Chr.	Position (bp)†	Gene	p Value	$r^{2‡}$
rs11227230	11	65356674	*EHBP1L1*	1.2×10^{-6}	0.96
rs1151503	11	65357697	*EHBP1L1*	1.3×10^{-6}	0.96
rs4326800	11	65367253	*MAP3K11*	1.9×10^{-6}	1.00
rs10791821	11	65368323	*MAP3K11*	1.9×10^{-6}	-
rs34278912	11	65360243	*KCNK7*	2.0×10^{-6}	0.91

Chr., chromosome.

*dbSNP rs number.

†SNP positions are based on NCBI human genome reference sequence Build 37.4.

‡r^2 indicates the pairwise linkage disequilibrium with rs10791821.

Supplementary Table S7A Univariate and multivariate logistic regression including three SNPs of *ABCG2*

	Univariate		Multivariate	
SNP*	OR (95% CI)	p Value†	OR (95% CI)	p Value†
rs2728125	2.06 (1.84 - 2.30)	2.3×10^{-36}	0.85 (0.68 - 1.08)	0.19
rs72552713	2.18 (1.63 - 2.92)	1.4×10^{-7}	2.95 (2.18 - 3.98)	1.9×10^{-12}
rs2231142	2.35 (2.11 - 2.63)	2.9×10^{-51}	2.83 (2.24 - 3.57)	1.8×10^{-18}

OR, odds ratio; CI, confidence interval.

*dbSNP rs number.

†We analyzed 1993 cases and 1334 controls whose genotype data for rs72552713 and rs223114 were available.

Supplementary Table S7B Association analysis of gout with *ABCG2* dysfunctional missense variants

					Freq.			
SNP*	Chr.	Position (bp)†	Amino Acid change	A1/A2‡	Cases	Controls	OR (95% CI)[d]	p Value§
rs72552713	4	89052957	Gln126Ter	T/C	0.049	0.023	2.86 (2.12 - 3.85)	4.4×10^{-12}
rs2231142	4	89052323	Gln141Lys	A/C	0.46	0.27	2.47 (2.20 - 2.76)	1.6×10^{-55}

Chr., chromosome; Freq., frequency of A1; OR, odds ratio; CI, confidence interval.

*dbSNP rs number.

†SNP positions are based on NCBI human genome reference sequence Build 37.4.

‡A1 is a risk-associated allele and A2 is a non-risk-associated allele.

§We analyzed 1993 cases and 1334 controls whose genotype data for these two SNPs were available. Logistic regression analyses were performed using a multivariate model including two SNPs, which located on different haplotypes.

Supplementary Table S8 Magnitude of gout risk associated with the number of risk alleles

Risk allele No.	Cases	Controls	OR (95% CI)[a]	p Value*
4 or less	45	134	Reference	
5	148	246	1.79 (1.21 - 2.66)	3.5×10^{-3}
6	377	355	3.16 (2.19 - 4.57)	2.3×10^{-10}
7	548	320	5.10 (3.54 - 7.34)	9.7×10^{-21}
8	507	149	10.1 (6.90 - 14.9)	5.3×10^{-39}
9 or more	265	46	18.6 (11.8 - 29.2)	3.6×10^{-45}

OR, odds ratio; CI, confidence interval.

*We analyzed 1937 cases and 1254 controls whose genotype data for the following six SNPs were available: rs3775948 of *SLC2A9*, rs2188380 of *MYL2-CUX2*, rs1260326 of *GCKR*, rs4073582 of *CNIH-2,* rs72552713 and rs2231142 of *ABCG2*.

Supplementary Table S9 Association analysis between seven SNPs and three uric acid-related parameters

		SUA[†]				FE_{UA}[‡]				UUE[‡]			
			95% CI				95% CI				95% CI		
SNP*	Gene	Coef.	LL	UL	p Value[§]	Coef.	LL	UL	p Value[§]	Coef.	LL	UL	p Value[§]
rs3775948	*SLC2A9*	0.166	0.076	0.256	**3.1×10^{-4}**	-0.260	-0.368	-0.152	**2.6×10^{-6}**	-0.809	-1.482	-0.136	**0.018**
rs2188380	*MYL2-CUX2*	0.074	-0.048	0.196	0.23	-0.141	-0.288	0.006	0.06	0.480	-0.437	1.396	0.30
rs1260326	*GCKR*	0.063	-0.019	0.146	0.13	-0.064	-0.164	0.034	0.20	0.127	-0.490	0.745	0.69
rs4073582	*CNIH-2*	-0.008	-0.187	0.171	0.93	-0.030	-0.245	0.184	0.78	0.224	-1.115	1.562	0.74
rs10791821	*MAP3K11*	0.032	-0.145	0.208	0.72	-0.076	-0.288	0.135	0.48	-0.792	-2.109	0.525	0.24
rs72552713	*ABCG2*	0.402	0.210	0.594	**4.3×10^{-5}**	0.348	0.116	0.579	**3.3×10^{-3}**	2.780	1.338	4.222	**1.6×10^{-4}**
rs2231142	*ABCG2*	0.183	0.098	0.268	**2.6×10^{-5}**	0.244	0.142	0.346	**3.2×10^{-6}**	1.862	1.224	2.500	**1.2×10^{-8}**

SUA, serum uric acid (unit: mg/dl); FE_{UA}, fractional excretion of urate clearance (unit: %); UUE, urinary urate excretion (unit: mg/hr/1.73m^2); Coef., regression coefficient; CI, confidence interval; LL, lower limit; UL, upper limit. We performed multivariate linear regression analyses, in which all 7 SNPs, alcohol drinking and BMI were included in the model.

*dbSNP rs number.

[†]Among 1657 gout patients with records of SUA, 1616 patients with complete information on all the explanatory variables were analyzed.

[‡]Among 1613 gout patients with records of FE_{UA} and UUE, 1574 patients with complete information on all the explanatory variables were analyzed.

[§]p values smaller than 0.05 are shown in bold letters.

Supplementary Table S10 Linkage disequilibrium among rs4073582 of *CNIH-2*, rs10791821 of *MAP3K11*, and rs504915 of *NRXN2*

		r^2		
		rs4073582 (*CNIH-2*)	rs10791821 (*MAP3K11*)	rs504915 (*NRXN2*)
D'	rs4073582 (*CNIH-2*)		0.010	0.006
	rs10791821 (*MAP3K11*)	0.124		0.189
	rs504915 (*NRXN2*)	0.728	0.649	

Supplementary Table S11 Multivariate logistic regression analysis adjusted with rs504915 of *NRXN2*

		Univariate		Multivariate†	
SNP*	Gene	p Value	OR (95% CI)	p Value	OR (95% CI)
rs4073582	*CNIH-2*	1.6×10^{-4}	1.55 (1.23-1.96)	3.3×10^{-4}	1.55 (1.22-1.96)
rs10791821	*MAP3K11*	3.4×10^{-3}	1.41 (1.12-1.77)	2.4×10^{-3}	1.44 (1.14-1.82)

OR, odds ratio; CI, confidence interval.

*dbSNP rs number.

†We performed multivariate logistic regression analyses using replication stage samples. These data were adjusted with rs504915 of *NRXN2*.

Supplementary Methods

Genotyping and quality control

At GWAS stage, the data sets were filtered individually on the basis of single nucleotide polymorphism (SNP) genotype missing call rates (>1%), and the Hardy-Weinberg equilibrium (HWE) in controls ($p<1.0\times10^{-6}$). We confirmed that all the subjects showed high genotype call rates (>98%). Pairwise identity by state was evaluated in order to identify pairs of individuals with cryptic relatedness. We confirmed that there was no pair showing cryptic relatedness greater than expected for second-degree relatives. We performed principal component analysis including our GWAS data set together with HapMap phase II samples.[1 2] As a result, we excluded one gout patient as a population outlier who was presumed to be of mixed origin (East Asian and European) (supplementary figure S2). Finally, 570 442 SNPs passed filters for 945 cases and 1213 controls.

One hundred twenty-three SNPs passing the significance threshold at $p<1.0\times10^{-5}$ in the GWAS stage were used for the subsequent analyses. For closely located SNPs, we detected top-ranked SNPs and then we examined the pairwise linkage disequilibrium (LD) between SNP showing the most significant association and other SNPs. For each novel risk locus, we confirmed that all of the SNPs showing associations at $p<1.0\times10^{-5}$ were in moderate to strong LD ($r^2>0.3$) with SNP showing the most significant association. Furthermore, these SNPs were no longer significant at $p<1.0\times10^{-5}$ after adjusting for the most significantly associated SNP in each locus by the logistic regression analyses. Finally, we selected 16 SNPs for replication study. We genotyped these SNPs and confirmed that all the 16 SNPs were of high call rate (>98%) and did not show significant deviation from HWE in controls ($p>0.05$).

Statistical analyses for GWAS

We conducted an association analysis using a 2×2 contingency table based on the allele frequency. For each of the filtered SNPs, p value of association was assessed by χ^2 test, and the odds ratio (OR) and 95% confidence interval (95% CI) were calculated. The quantile-quantile plot and the genomic inflation factor (λ) were used to assess the presence of systematic bias in the test statistics due to potential population stratification. After excluding SNPs within 500 kb from the SNPs reaching a genome-wide significance threshold ($p<5.0\times10^{-8}$), the λ was 1.054, indicating a subtle inflation of p values (supplementary figure S3).

Imputation

For the imputation, the 1000 genomes reference panel (the East Asian population) was obtained from the phase 1 release (16 March 2012, http://www.1000genomes.org/announcements/updated-integrated-phase-1-release-calls-2012-03-16), and we ran a logistic regression analysis based on imputation dosages via MACH2DAT.[3] We included all SNPs with estimated $r^2>0.9$ and minor allele frequency ≥ 0.01 for analysis.

Analysis of the two dysfunctional SNPs of *ABCG2*

The genotyping of the two *ABCG2* SNPs (rs72552713 and rs2231142) was performed with an allelic discrimination assay (Custom TaqMan Assay, Applied Biosystems) with a LightCycler 480 (Roche

Diagnostics).[4] All the logistic regression analyses were performed with a software SPSS v.22.0J (IBM Japan Inc.). A software R (version 3.0.2) (http://www.r-project.org/) with GenABEL software package was used for LD analysis.

Estimation of variance explained by identified SNPs

For each variant identified in our GWAS, we calculated percent of the variance explained. We used the liability threshold model in quantitative genetics.[5] In this model, it is assumed that liability of a binary disease trait on unobserved continuous scale is assumed to be normally distributed with a mean of zero and variance of one, and individuals whose liabilities surpass a threshold develop the disease. To calculate the percent variance explained, we assumed that the prevalence of gout was 1.1% based on the estimation in Japanese male population.[4 6] We assumed that SNP effects were additive on the logistic scale. Under the rare disease assumption, we approximated the relative risk by the odds ratio obtained in this study. For the identified SNPs, we used the allele frequencies in the East Asian population in the 1000 Genomes Project.[7]

Subtype analysis

We investigated the magnitude of associations between the identified SNPs and the types of gout by examining type-specific ORs and the case-subtype heterogeneity test. Fractional excretion of urate clearance (FE_{UA}) and urinary urate excretion (UUE) were measured for each patient as described previously,[8] and all cases were classified based on the criteria (supplementary figure S1). To estimate gout type-specific ORs, the frequency of a SNP in each type was compared with the frequency in controls using a logistic regression. To assess whether the estimated type-specific ORs were significantly different, the frequencies of the SNP were compared between types by dichotomous logistic regression (the case-subtype heterogeneity test).[9] For these subtype analyses, the effects of alcohol drinking, body mass index (BMI), and all the identified SNPs were considered in the model. When evaluating the effects of risk allele of SNP on clinical parameters (FE_{UA} and UUE), a linear regression analysis was performed by defining the SNP genotype predictor variable x as the number of risk alleles associated with gout risk. All the logistic and linear regression analyses were performed using the STATA version 11.0.

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