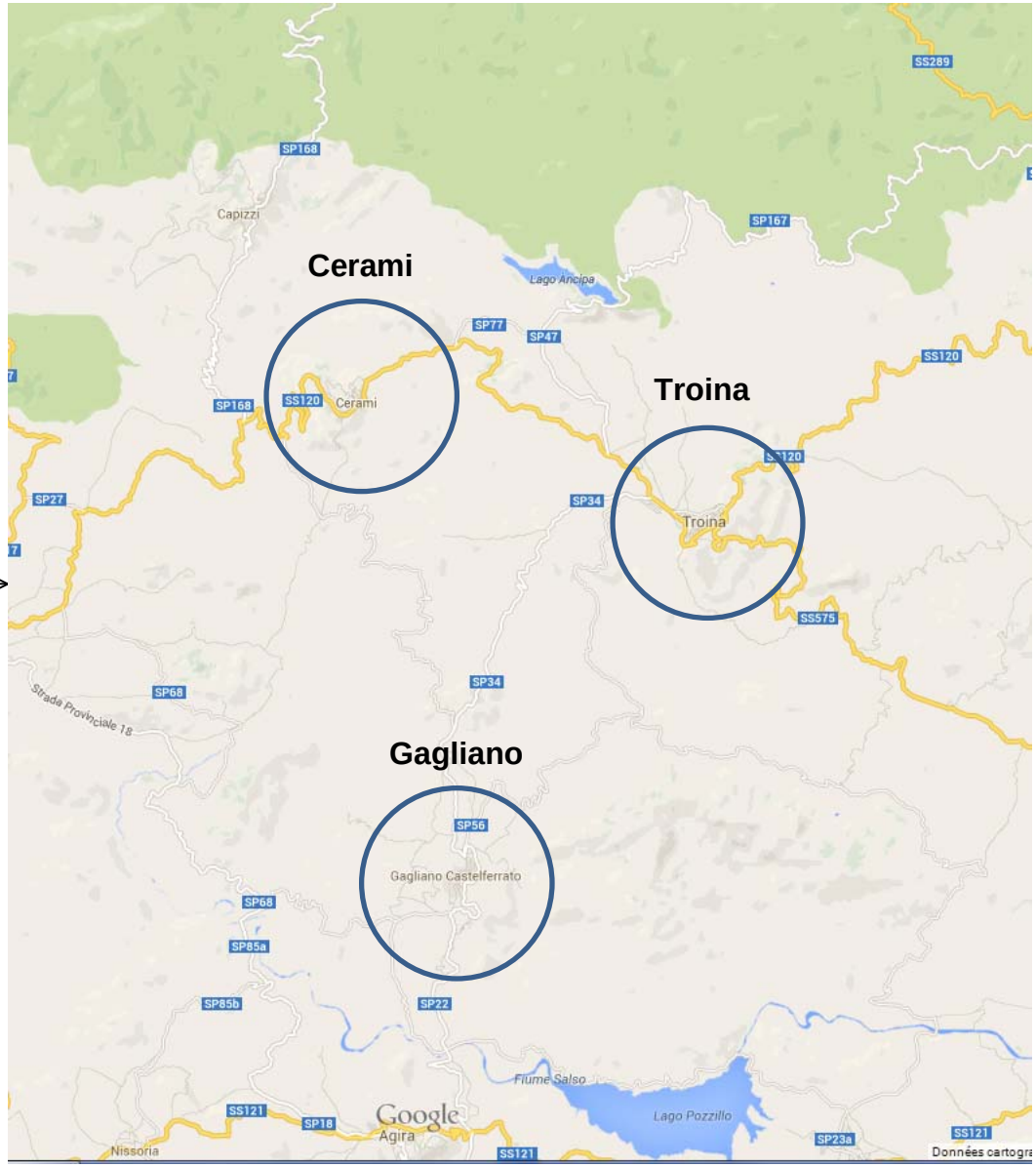
OASI Cohort[1,2,3]

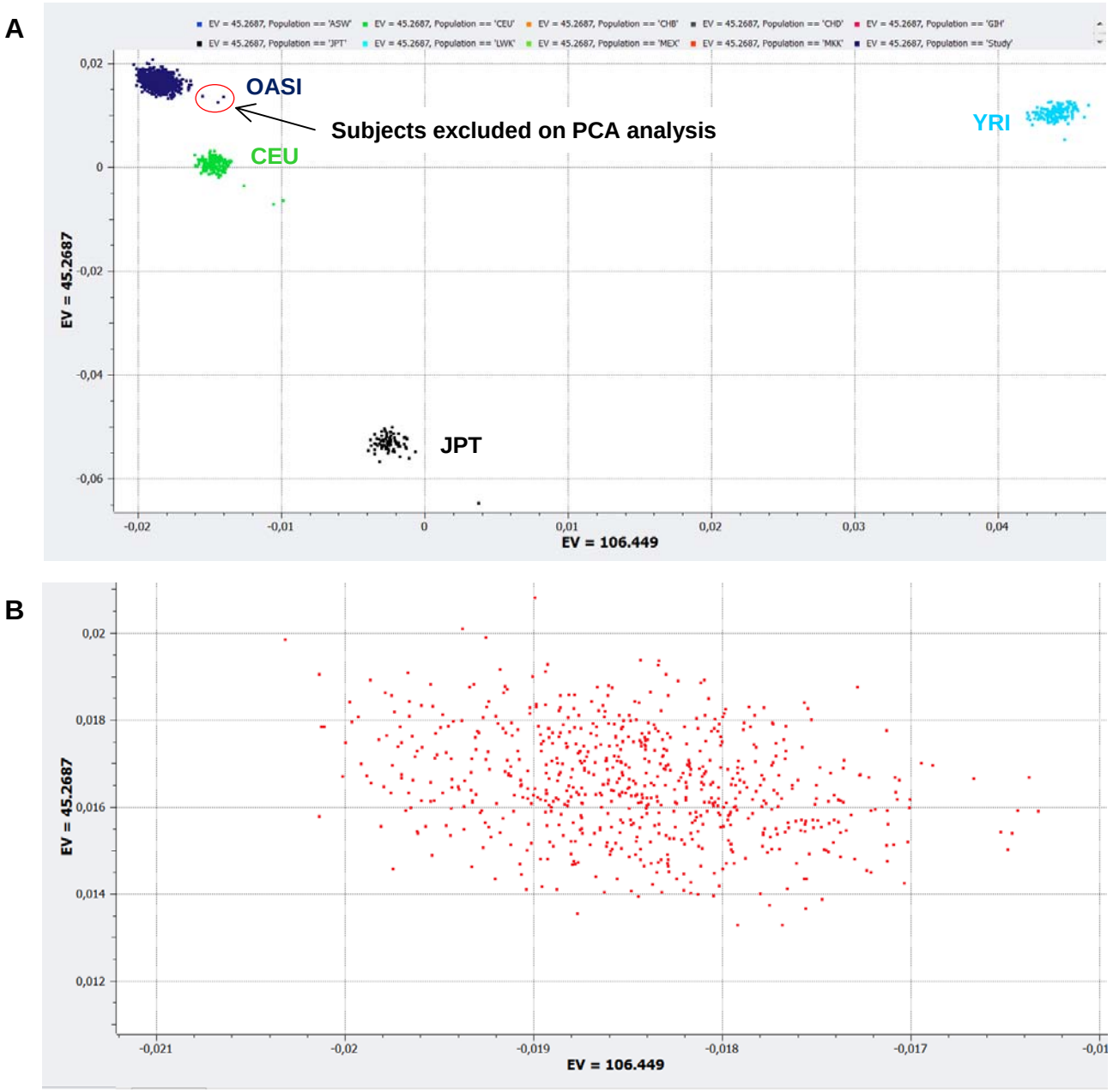
- Troina
- Cerrami
- Gagloani castalferrato



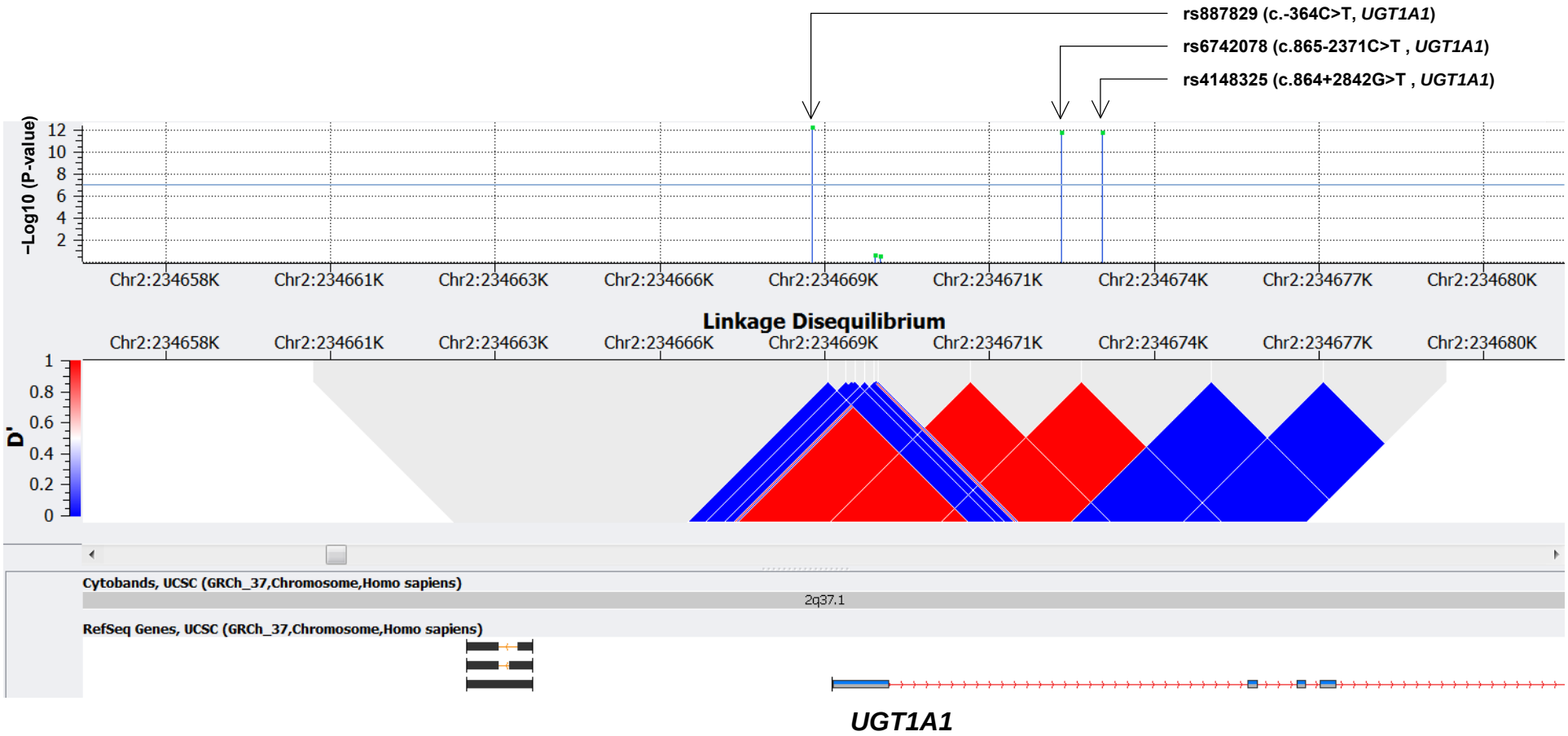
1. Gueant-Rodriguez RM, *et al*. Am J Clin Nutr 2006;83:701-7.
2. Gueant JL, *et al*. J Med Genet 2007;44:363-7.
3. Oussalah A, *et al*. Am J Clin Nutr 2012;95:514-21.

Supplementary Figure S1 **OA_Supplemental Digital Content**

Figure 1. The OASI cohort design. Between January 1999 and December 2006, ambulatory subjects were included from three communes from Sicily, Italy in the same Province of Enna: Troina, Cerami, and Gagliano Castelferrato (the OASI cohort Sicily)

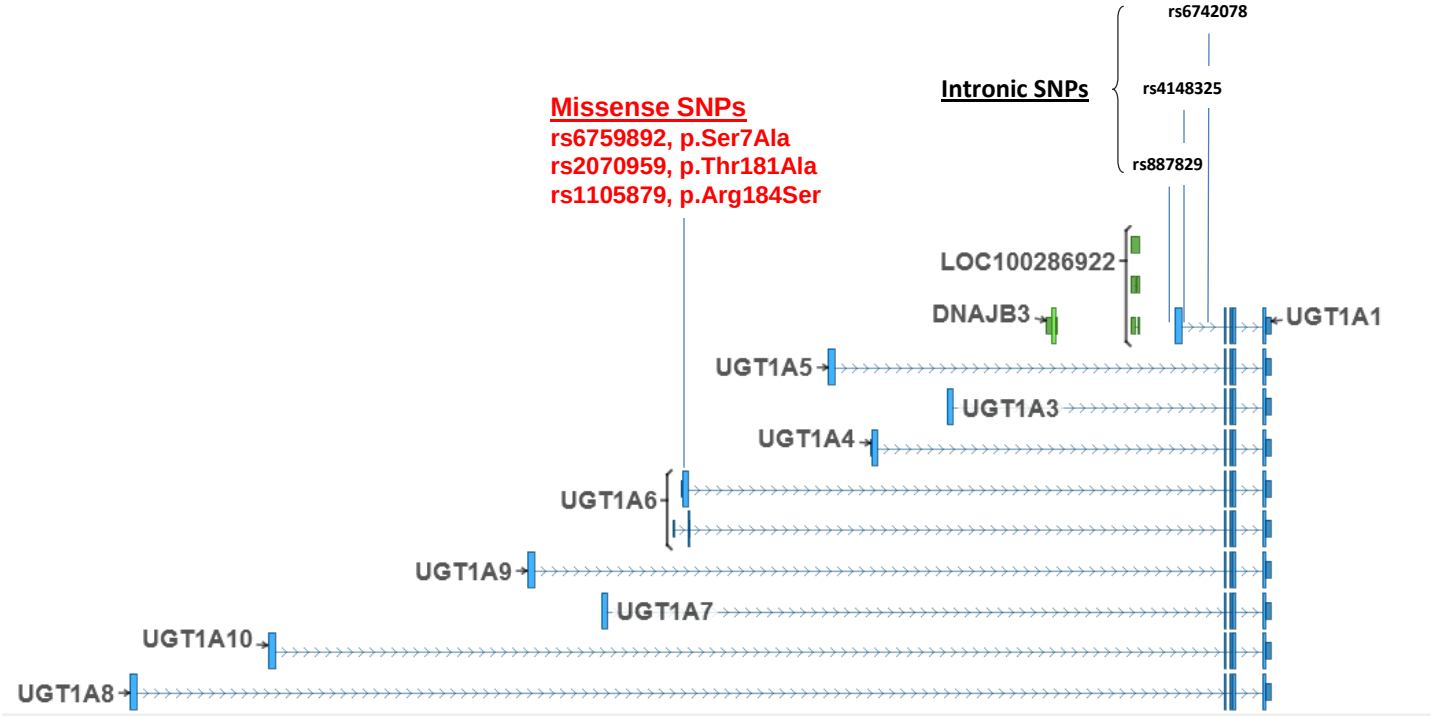


Supplementary Figure S2 **OA_Supplemental Digital Content Figure 2.** Principal-component analysis (PCA) was performed on the study samples merged with HapMap phase 3 populations as reference populations to identify ancestry outliers. (Dark blue dots = study population subjects; green dots = Utah Residents (CEPH) with Northern and Western European ancestry population subjects; dark dots = Japanese in Tokyo, Japan and Han Chinese in Bejing, China populations subjects; light blue dots = Yoruba in Ibadan, Nigeria population subjects), (b) Principal-component analysis (PCA) after exclusion of outlier subjects (n=3).

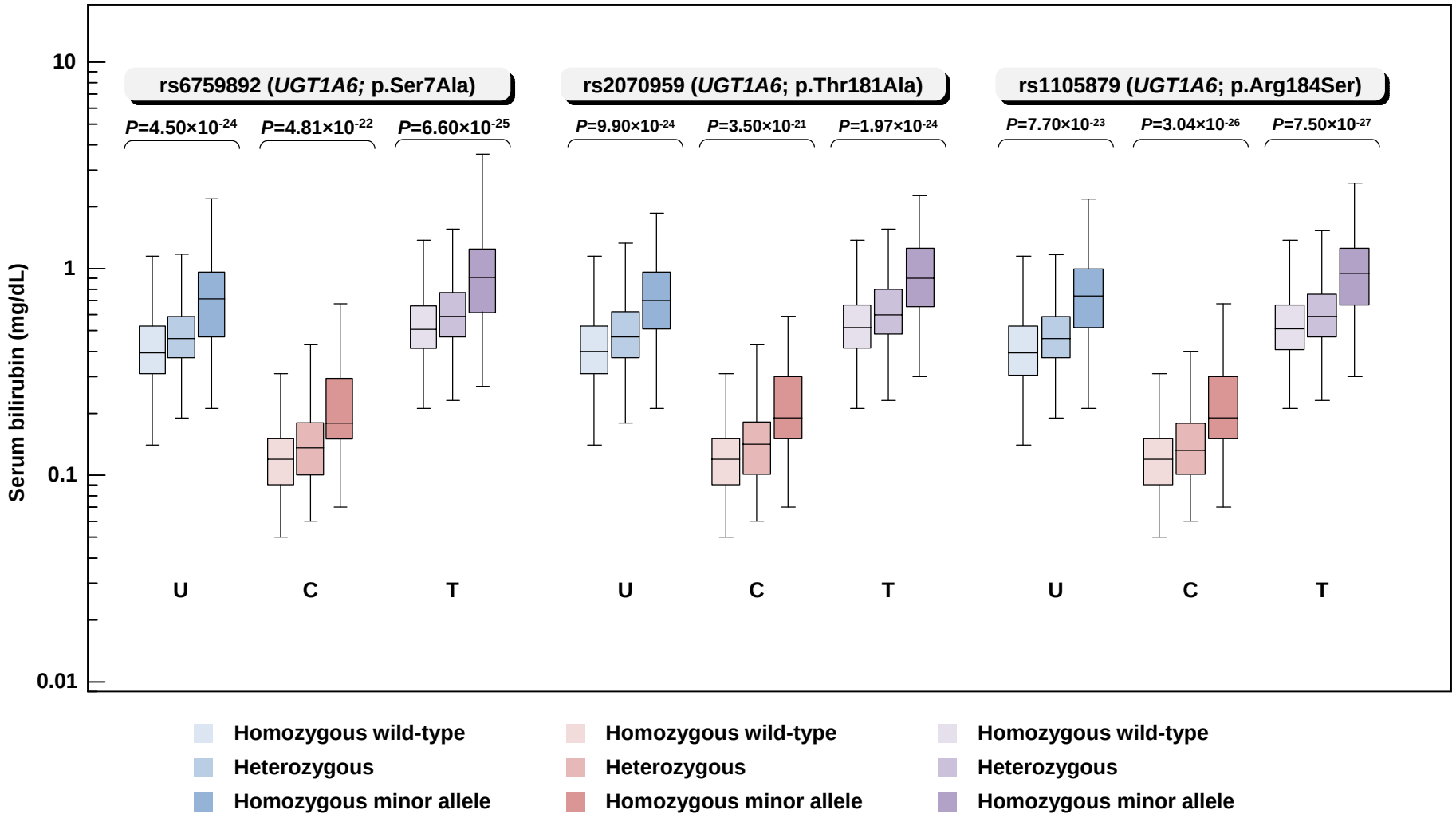


Supplementary Figure S3 **OA_Supplemental Digital Content Figure 3.** Manhattan plot on 2q37.1 with linkage disequilibrium plot and cytobands according to UCSC (GRCh_37) of the three intronic *UGT1A1* SNPs significantly associated with unconjugated, conjugated, and total serum bilirubin level in the initial study (n=400). Association results of the single-variant analysis (−log10 P, total bilirubin) are plotted against genomic position (National Center for Biotechnology Information build 37). Bottom, genes within the region of interest are annotated, with arrows indicating the direction of transcription. Linkage disequilibrium (D' values) between the lead SNP and the other SNPs are indicated by color. The blue horizontal line indicates the significance threshold for genome-wide association.

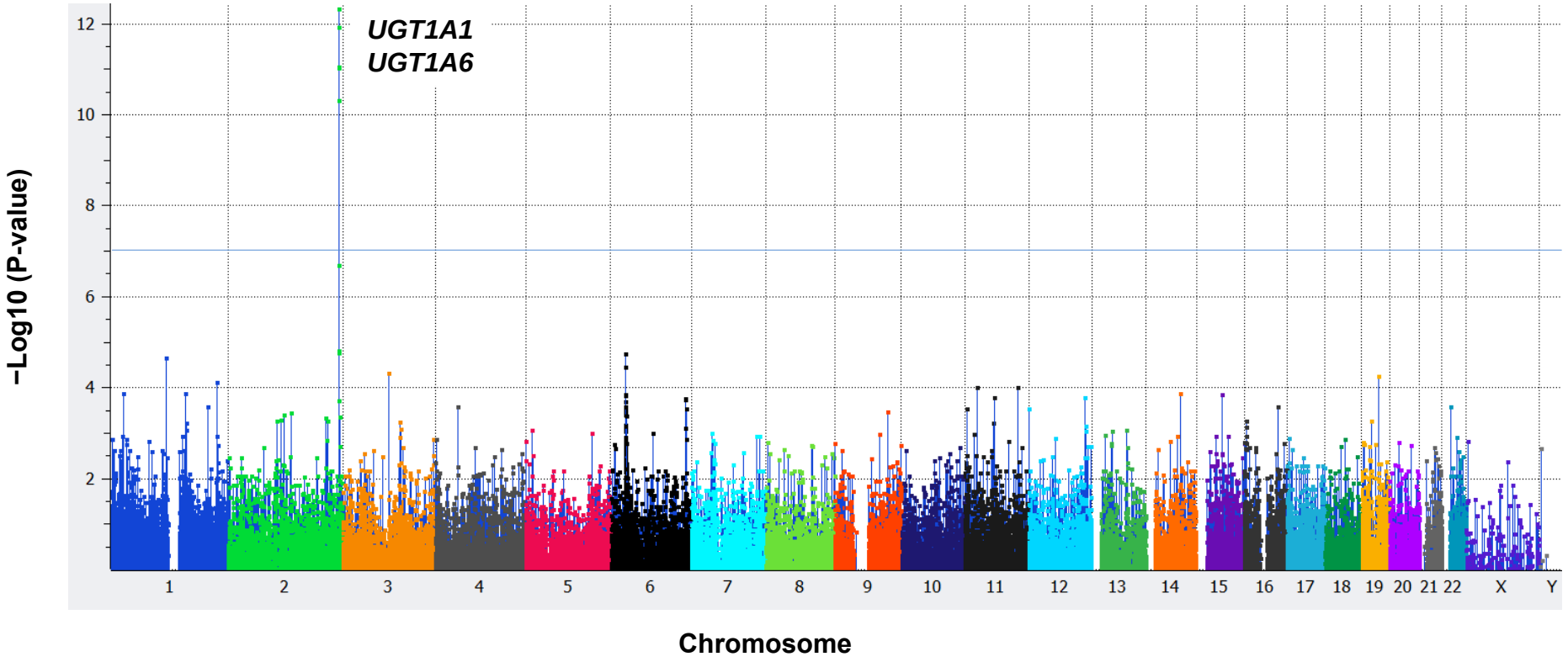
Supplementary Figure S4 **OA_Supplemental Digital Content Figure 4.** Manhattan plot on 2q37.1 with linkage disequilibrium plot and cytobands according to UCSC (GRCh_37) showing the three intronic *UGT1A1* SNPs and the 3 exonic *UGT1A6* SNPs significantly associated with unconjugated, conjugated, and total serum bilirubin level in initial and *in silico* replication pooled studies (n=773). Association results of the single-variant analysis (−log10 P, total bilirubin) are plotted against genomic position (National Center for Biotechnology Information build 37). Bottom, genes within the region of interest are annotated, with arrows indicating the direction of transcription. Linkage disequilibrium (D' values) between the lead SNP and the other SNPs are indicated by color. The blue horizontal line indicates the significance threshold for genome-wide association.



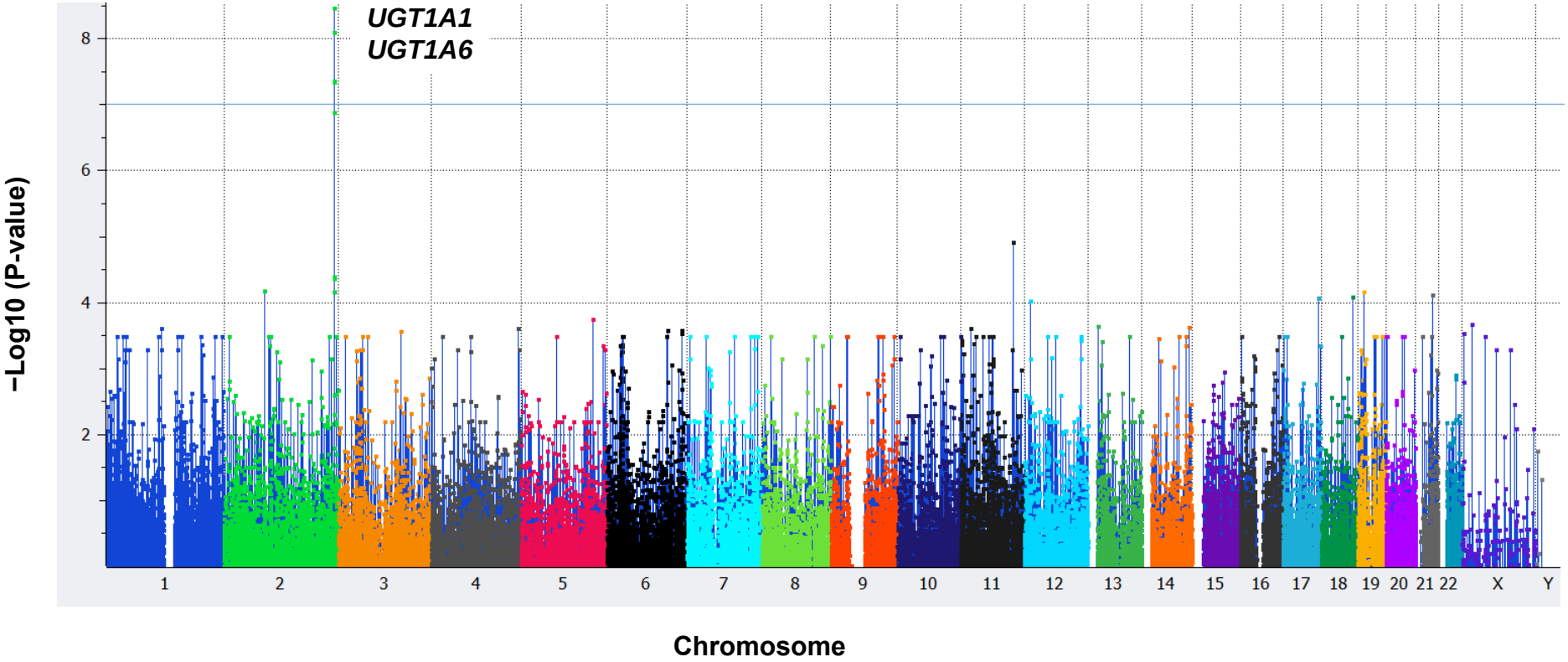
Supplementary Figure S5 **OA_Supplemental Digital Content Figure 5.** (A) Genomic position of the three SNPs: rs6759892 (c.19T>G, p.Ser7Ala), rs2070959 (c.541A>G, p.Thr181Ala), and rs1105879 (c.552A>C, p.Arg184Ser) on the first exon of the *UGT1A6* gene (Illustration used the Golden Helix Genome Browse 1.1.2 software). (B) Genomic position of the three intronic SNPs of the *UGT1A1* gene and the three exonic SNPs on the first exon of *UGT1A6* [rs6759892 (c.19T>G, p.Ser7Ala), rs2070959 (c.541A>G, p.Thr181Ala), and rs1105879 (c.552A>C, p.Arg184Ser)] in the UDP-glucuronosyltransferases *UGT1A* complex locus (illustration used the Golden Helix Genome Browse 1.1.2 software).



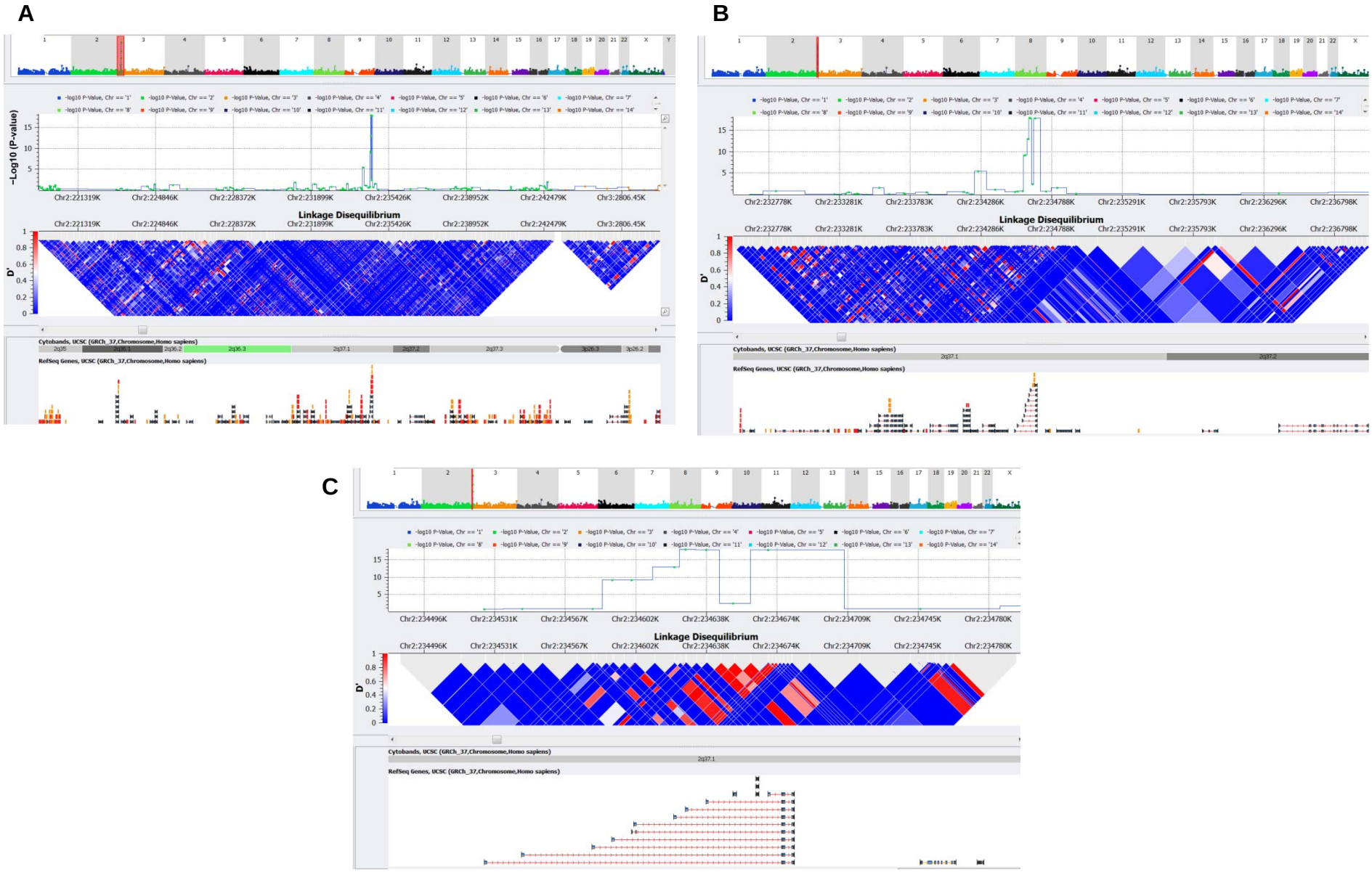
Supplementary Figure S6 **OA_Supplemental Digital Content Figure 6.** Median unconjugated, conjugated, and total serum bilirubin level according to *UGT1A1* and *UGT1A6* variants (U: unconjugated serum bilirubin, C: conjugated serum bilirubin, T: total serum bilirubin). Kruskal-Wallis test *P*-values are reported for the total serum bilirubin level.



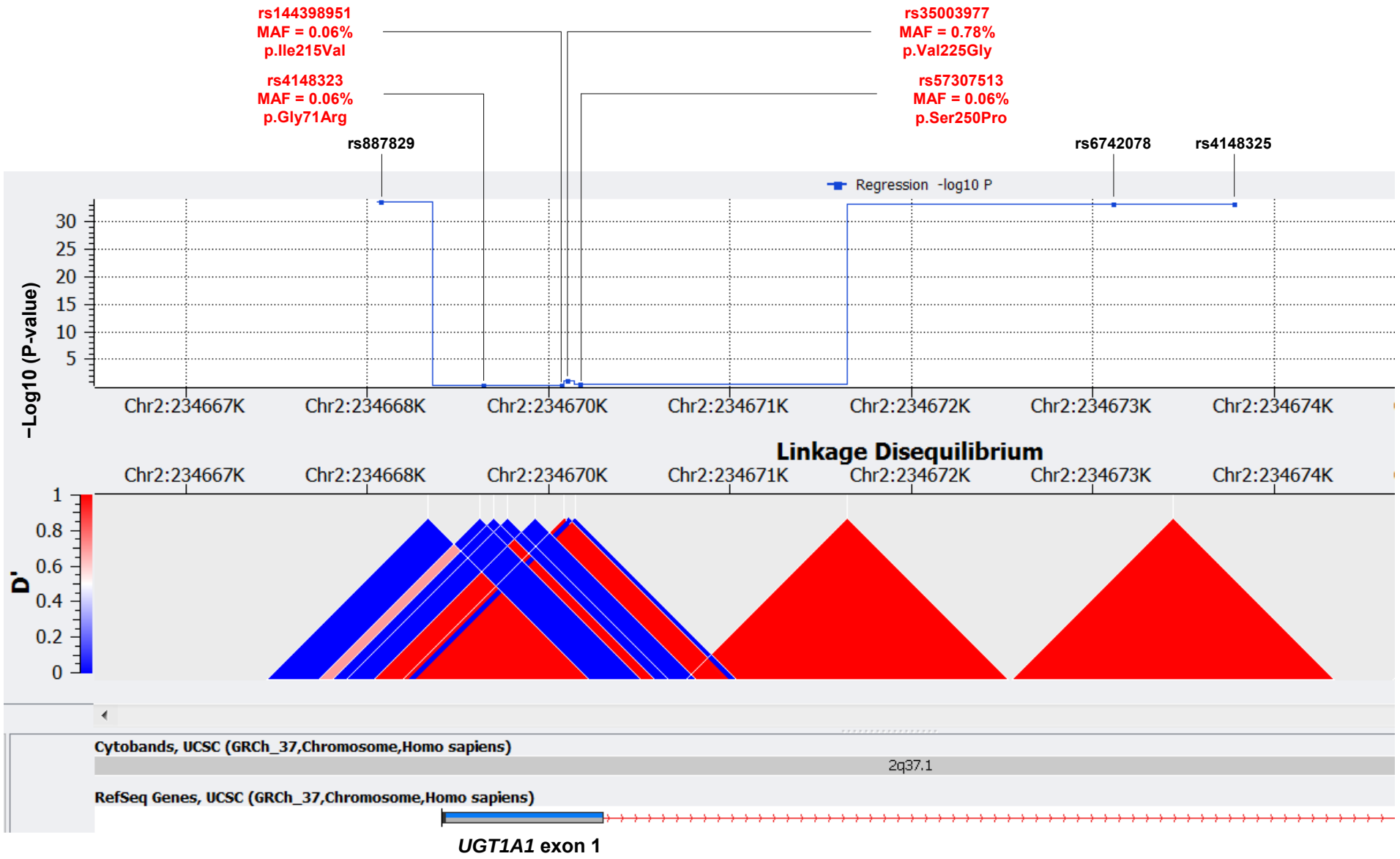
Supplementary Figure S7 **OA_Supplemental Digital Content Figure 7.** Manhattan plot for unconjugated serum bilirubin level. Association results of the single-variant analysis (−log10 P) are plotted against genomic position (National Center for Biotechnology Information build 37). The blue horizontal line indicates the significance threshold for genome-wide association.



Supplementary Figure S8 **OA_Supplemental Digital Content Figure 8.** Manhattan plot for conjugated serum bilirubin level. Association results of the single-variant analysis (−log10 P) are plotted against genomic position (National Center for Biotechnology Information build 37). The blue horizontal line indicates the significance threshold for genome-wide association.



Supplementary Figure S9 **OA_Supplemental Digital Content Figure 9.** Manhattan plot from 2q35 to 2q37.3 with linkage disequilibrium plot and cytobands according to UCSC (GRCh_37) reporting the gene-based combined multivariate and collapsing method analysis. Association results of the single-gene analysis (−log10 P) are plotted against genomic position (National Center for Biotechnology Information build 37). Bottom, genes within the region of interest are annotated, with arrows indicating the direction of transcription. Linkage disequilibrium (D' values) between the lead SNP and the other SNPs are indicated by color (A, B, and C panels show the progressive zoomed view to *UGT1A* gene complex in 2q37.1.



Supplementary Figure S10 **OA_Supplemental Digital Content Figure 10.** Manhattan plot on 2q37.1 with linkage disequilibrium plot and cytobands according to UCSC (GRCh_37) showing the three intronic *UGT1A1* SNPs significantly associated with unconjugated, conjugated, and total serum bilirubin level that are in strong linkage disequilibrium with the 4 low-frequency coding variants located in the first exon of *UGT1A1*. Association results of the single-variant analysis (−log10 P) are plotted against genomic position (National Center for Biotechnology Information build 37). Bottom, genes within the region of interest are annotated, with arrows indicating the direction of transcription. Linkage disequilibrium (D' values) between the lead SNP and the other SNPs are indicated by color.

Supplementary Table S1. Clinical characteristics of the participants included in the study

	Initial (n=400)		***In silico* Replication (n=373)**		**Replication (n=227)**		**Pooled studies (n=1000)**	
	Median	**IQR, 25 – 75th**	**Median**	**IQR, 25 – 75th**	**Median**	**IQR, 25 – 75th**	**Median**	**IQR, 25 – 75th**
Age at inclusion	72	66 – 76	71	66 – 77	73	68 – 79	72	66 – 77
Total bilirubin (mg/dL)	0.60	0.46 – 0.85	0.55	0.45 – 0.75	0.61	0.45 – 0.81	0.58	0.45 – 0.80
Unconjugated bilirubin (mg/dL)	0.49	0.37 – 0.68	0.41	0.33 – 0.57	0.43	0.32 – 0.58	0.44	0.34 – 0.62
Conjugated bilirubin (mg/dL)	0.12	0.09 – 0.17	0.15	0.12 – 0.19	0.17	0.13 – 0.23	0.14	0.11 – 0.19
	%	**95%, CI**	**%**	**95%, CI**	**%**	**95%, CI**	**%**	**95%, CI**
Male gender	42.3	37.4 – 47.1	42.9	37.8 – 47.9	40.5	34.1 – 47.0	42.0	39.0 – 45.2

NOTE. IQR: interquartile range.

Supplementary Table S2. Functional annotation and quality controls of the variants associated with serum total bilirubin level in the Oasi cohort subjects

Marker	Chr.	Position[a]	Gene	HGVS	AA substitution	Functional	Strand	Observed	Strand Versus dbSNP	dbSNP Strand	Call Rate	Minor Allele	MAF	Fisher's HWE *P*-value
	Initial study (n=400)													
rs6759892	2	234601669	*UGT1A6*	c.19T>G	p.Ser7Ala	missense	Top	A/C	reverse	T/G	0.9975	C	0.3634	0.3864
rs2070959	2	234602191	*UGT1A6*	c.541A>G	p.Thr181Ala	missense	Bot	T/C	reverse	A/G	0.9975	G	0.3271	0.3625
rs1105879	2	234602202	*UGT1A6*	c.552A>C	p.Arg184Ser	missense	Bot	T/G	reverse	A/C	0.9925	C	0.3589	0.2298
rs887829	2	234668570	*UGT1A1*	c.-364C>T	—	nearGene-5	Top	A/G	same	A/G	0.9975	A	0.3283	0.1128
rs6742078	2	234672639	*UGT1A1*	c.864+2842G>T	—	intronic	Top	A/C	reverse	T/G	1	A	0.3313	0.1142
rs4148325	2	234673309	*UGT1A1*	c.865-2371C>T	—	intronic	Bot	T/C	same	T/C	1	A	0.3313	0.1142
	***In silico* replication study (n=373)**													
rs6759892	2	234601669	*UGT1A6*	c.19T>G	p.Ser7Ala	missense	Top	A/C	reverse	T/G	1.0000	C	0.3834	0.2734
rs2070959	2	234602191	*UGT1A6*	c.541A>G	p.Thr181Ala	missense	Bot	T/C	reverse	A/G	1.0000	G	0.3445	0.1357
rs1105879	2	234602202	*UGT1A6*	c.552A>C	p.Arg184Ser	missense	Bot	T/G	reverse	A/C	0.9786	C	0.3699	0.1163
rs887829	2	234668570	*UGT1A1*	c.-364C>T	—	nearGene-5	Top	A/G	same	A/G	1.0000	A	0.3405	0.5641
rs6742078	2	234672639	*UGT1A1*	c.864+2842G>T	—	intronic	Top	A/C	reverse	T/G	0.9973	A	0.3401	0.4894
rs4148325	2	234673309	*UGT1A1*	c.865-2371C>T	—	intronic	Bot	T/C	same	T/C	1.0000	A	0.3405	0.5641
	Pooled analysis from initial and replication studies (n=773)													
rs6759892	2	234601669	*UGT1A6*	c.19T>G	p.Ser7Ala	missense	Top	A/C	reverse	T/G	0.9987	C	0.3731	0.1440
rs2070959	2	234602191	*UGT1A6*	c.541A>G	p.Thr181Ala	missense	Bot	T/C	reverse	A/G	0.9987	G	0.3355	0.0758
rs1105879	2	234602202	*UGT1A6*	c.552A>C	p.Arg184Ser	missense	Bot	T/G	reverse	A/C	0.9858	C	0.3642	0.0423
rs887829	2	234668570	*UGT1A1*	c.-364C>T	—	nearGene-5	Top	A/G	same	A/G	0.9987	A	0.3342	0.1241
rs6742078	2	234672639	*UGT1A1*	c.864+2842G>T	—	intronic	Top	A/C	reverse	T/G	0.9987	A	0.3355	0.1065
rs4148325	2	234673309	*UGT1A1*	c.865-2371C>T	—	intronic	Bot	T/C	same	T/C	1.0000	A	0.3357	0.1076

NOTE. Chr: chromosome; HGVS: Human genome variation society; AA: amino acid; MAF: minor allele frequency; HWE: Hardy-Weinberg equilibrium.

a: Position according to Genome Reference Consortium GRCh37 (hg19; Feb. 2009) coordinates.

Supplementary Table S3. Linkage disequilibrium pairwise analysis matrix

LD EM R-squared					
Marker	**rs6759892**	**rs2070959**	**rs1105879**	**rs887829**	**rs6742078**
rs2070959	0.848456314	—	—	—	—
rs1105879	0.961129947	0.878133412	—	—	—
rs887829	0.721934641	0.727734161	0.732096486	—	—
rs6742078	0.716061344	0.722301209	0.728515107	0.994191637	—
rs4148325	0.716450419	0.722707717	0.726614559	0.994200978	1
LD EM D-prime					
Marker	**rs6759892**	**rs2070959**	**rs1105879**	**rs887829**	**rs6742078**
rs2070959	0.999993337	—	—	—	—
rs1105879	0.997107567	0.999997107	—	—	—
rs887829	0.925111778	0.855557666	0.915764411	—	—
rs6742078	0.918781964	0.849883056	0.909632125	0.999999998	—
rs4148325	0.918915198	0.850122178	0.909642075	0.999999998	1

Supplemental Table S4. Variants associated at the exome-wide level with the total, unconjugated, and conjugated bilirubin level in the Troina cohort subjects (n=773) after adjusting for age and gender

Variant	Chromosome	Position	FvR Model P-Value*	Bonferroni P-value	Slope	Slope SE	Full-Model R Squared
Total bilirubin							
rs6759892	2	234601669	1.27×10^{-23}	8.60×10^{-19}	0.107	0.010	0.163
rs2070959	2	234602191	1.63×10^{-24}	1.10×10^{-19}	0.111	0.010	0.168
rs1105879	2	234602202	2.80×10^{-26}	1.89×10^{-21}	0.114	0.010	0.178
rs887829	2	234668570	5.56×10^{-31}	3.75×10^{-26}	0.125	0.010	0.199
rs6742078	2	234672639	1.29×10^{-30}	8.73×10^{-26}	0.124	0.010	0.199
rs4148325	2	234673309	1.13×10^{-30}	7.64×10^{-26}	0.124	0.010	0.198
Unconjugated bilirubin							
rs6759892	2	234601669	1.69×10^{-24}	1.14×10-19	0.117	0.011	0.164
rs2070959	2	234602191	4.29×10^{-26}	2.90×10^{-21}	0.123	0.011	0.172
rs1105879	2	234602202	2.79×10^{-28}	1.88×10^{-23}	0.127	0.011	0.184
rs887829	2	234668570	2.65×10^{-34}	1.79×10^{-29}	0.141	0.011	0.211
rs6742078	2	234672639	5.08×10^{-34}	3.43×10^{-29}	0.140	0.011	0.211
rs4148325	2	234673309	4.41×10^{-34}	2.97×10^{-29}	0.141	0.011	0.210
Conjugated bilirubin							
rs6759892	2	234601669	1.10×10^{-22}	7.40×10^{-18}	0.101	0.010	0.170
rs2070959	2	234602191	1.96×10^{-22}	1.32×10^{-17}	0.102	0.010	0.169
rs1105879	2	234602202	1.66×10^{-23}	1.12×10^{-18}	0.103	0.010	0.177
rs887829	2	234668570	2.35×10^{-27}	1.59×10^{-22}	0.114	0.010	0.193
rs6742078	2	234672639	1.00×10^{-26}	6.77×10^{-22}	0.112	0.010	0.191
rs4148325	2	234673309	8.79×10^{-27}	5.94×10^{-22}	0.112	0.010	0.190

NOTE. FvR: full versus reduced model; SE: standard error

Supplementary Table S5. Median bilirubin values according to genotypes subgroups for the six exome-wide significant variants associated with unconjugated, conjugated, and total serum bilirubin level

	N	Median	25 - 75 P	N	Median	25 - 75 P	N	Median	25 - 75 P	H-statistic	*P*-value[a]	Bonf. *P*-value
	Genotype dd			Genotype Dd			Genotype DD					
	rs6759892 (*UGT1A6*; c.19T>G; missense; p.Ser7Ala)											
Unconjugated bilirubin (mg/dL)	313	**0.39**	0.31 to 0.53	342	**0.46**	0.37 to 0.59	117	**0.71**	0.47 to 0.97	107.52	4.50×10^{-24}	3.15×10^{-23}
Conjugated bilirubin (mg/dL)	312	**0.12**	0.09 to 0.15	342	**0.12**	0.10 to 0.18	117	**0.18**	0.15 to 0.29	98.17	4.81×10^{-22}	2.88×10^{-21}
Total bilirubin (mg/dL)	313	**0.51**	0.41 to 0.67	342	**0.59**	0.47 to 0.76	117	**0.92**	0.63 to 1.27	111.35	6.60×10^{-25}	4.62×10^{-24}
	rs2070959 (*UGT1A6*; c.541A>G; missense; p.Thr181Ala)											
Unconjugated bilirubin (mg/dL)	352	**0.40**	0.31 to 0.53	322	**0.47**	0.37 to 0.62	98	**0.70**	0.51 to 0.97	105.94	9.90×10^{-24}	6.93×10^{-23}
Conjugated bilirubin (mg/dL)	351	**0.12**	0.09 to 0.15	322	**0.14**	0.10 to 0.18	98	**0.19**	0.15 to 0.30	94.21	3.50×10^{-21}	2.10×10^{-20}
Total bilirubin (mg/dL)	352	**0.51**	0.41 to 0.67	322	**0.60**	0.48 to 0.79	98	**0.90**	0.65 to 1.27	109.17	1.97×10^{-24}	1.38×10^{-23}
	rs1105879 (*UGT1A6*; c.552A>C; missense; p.Arg184Ser)											
Unconjugated bilirubin (mg/dL)	321	**0.39**	0.31 to 0.52	327	**0.46**	0.37 to 0.59	114	**0.74**	0.52 to 1.00	101.84	7.70×10^{-23}	4.62×10^{-22}
Conjugated bilirubin (mg/dL)	320	**0.12**	0.09 to 0.15	327	**0.13**	0.10 to 0.18	114	**0.19**	0.15 to 0.30	117.51	3.04×10^{-26}	2.12×10^{-25}
Total bilirubin (mg/dL)	321	**0.51**	0.41 to 0.67	327	**0.59**	0.47 to 0.76	114	**0.96**	0.66 to 1.27	120.31	7.5×10^{-27}	5.25×10^{-26}
	rs887829 (*UGT1A1*; c.-364C>T; intronic)											
Unconjugated bilirubin (mg/dL)	352	**0.39**	0.30 to 0.51	324	**0.46**	0.38 to 0.62	96	**0.77**	0.60 to 1.06	144.72	3.75×10^{-32}	2.63×10^{-31}
Conjugated bilirubin (mg/dL)	351	**0.12**	0.09 to 0.15	324	**0.14**	0.11 to 0.18	96	**0.20**	0.16 to 0.30	115.66	7.68×10^{-26}	4.61×10^{-25}
Total bilirubin (mg/dL)	352	**0.51**	0.40 to 0.66	324	**0.61**	0.48 to 0.80	96	**0.97**	0.75 to 1.28	142.03	1.44×10^{-31}	1.01×10^{-30}
	rs6742078 (*UGT1A1*; c.864+2842G>T; intronic)											
Unconjugated bilirubin (mg/dL)	351	**0.39**	0.30 to 0.51	324	**0.46**	0.37 to 0.62	97	**0.74**	0.58 to 1.05	143.41	7.22×10^{-32}	5.06×10^{-31}
Conjugated bilirubin (mg/dL)	350	**0.12**	0.09 to 0.15	324	**0.14**	0.11 to 0.18	97	**0.19**	0.16 to 0.30	112.55	3.63×10^{-25}	2.18×10^{-24}
Total bilirubin (mg/dL)	351	**0.51**	0.40 to 0.66	324	**0.61**	0.48 to 0.79	97	**0.96**	0.74 to 1.28	140.37	3.30×10^{-31}	2.31×10^{-30}
	rs4148325 (*UGT1A1*; c.865-2371C>T; intronic)											
Unconjugated bilirubin (mg/dL)	351	**0.39**	0.30 to 0.51	325	**0.460**	0.37 to 0.62	97	**0.74**	0.58 to 1.05	143.47	7.02×10^{-32}	4.91×10^{-31}
Conjugated bilirubin (mg/dL)	350	**0.12**	0.09 to 0.15	325	**0.140**	0.11 to 0.18	97	**0.19**	0.16 to 0.30	112.64	3.48×10^{-25}	2.09×10^{-24}
Total bilirubin (mg/dL)	351	**0.51**	0.40 to 0.66	325	**0.610**	0.48 to 0.79	97	**0.96**	0.74 to 1.28	140.47	3.15×10^{-31}	2.20×10^{-30}

NOTE. N: number of subjects; Bonf: Bonferroni; 25 – 25 P: 25^{th} – 75^{th} percentile; D: minor allele; d: major allele.

a: Kruskal-Wallis test.

Supplementary Table S6. Variants associated at the exome-wide level with the serum unconjugated bilirubin level in the Oasi cohort subjects

Marker	Regression *P*-value	Regression Bonf. *P*-value	Regression Slope	Regression Slope SE	Corr/Trend *P*-value	Corr/Trend Bonf. *P*-value	Corr/Trend R
	Initial study (n=400)						
rs6759892	4.75×10^{-11}	2.62×10^{-6}	0.0963	0.0142	1.41×10^{-10}	7.75×10^{-6}	0.3216
rs2070959	9.17×10^{-12}	5.05×10^{-7}	0.1020	0.0145	3.22×10^{-11}	1.77×10^{-6}	0.3326
rs1105879	9.02×10^{-12}	4.96×10^{-7}	0.0996	0.0142	3.19×10^{-11}	1.75×10^{-6}	0.3336
rs887829	4.58×10^{-13}	2.52×10^{-8}	0.1062	0.0142	2.25×10^{-12}	1.24×10^{-7}	0.3518
rs6742078	1.16×10^{-12}	6.40×10^{-8}	0.1040	0.0142	5.11×10^{-12}	2.81×10^{-7}	0.3456
rs4148325	1.16×10^{-12}	6.40×10^{-8}	0.1040	0.0142	5.11×10^{-12}	2.81×10^{-7}	0.3456
	***In silico* replication study (n=373)**						
rs6759892	3.84×10^{-15}	2.69×10^{-14}	0.1398	0.0170	4.07×10^{-14}	2.85×10^{-13}	0.3919
rs2070959	6.54×10^{-16}	4.58×10^{-15}	0.1453	0.0172	9.09×10^{-15}	6.36×10^{-14}	0.4019
rs1105879	7.38×10^{-18}	5.16×10^{-17}	0.1538	0.0170	2.33×10^{-16}	1.63×10^{-15}	0.4300
rs887829	3.05×10^{-23}	2.14×10^{-22}	0.1792	0.0168	1.12×10^{-20}	7.84×10^{-20}	0.4834
rs6742078	3.60×10^{-23}	2.52×10^{-22}	0.1785	0.0168	1.29×10^{-20}	9.03×10^{-20}	0.4833
rs4148325	3.05×10^{-23}	2.14×10^{-22}	0.1792	0.0168	1.12×10^{-20}	7.84×10^{-20}	0.4834
	Pooled analysis from initial and replication studies (n=773)						
rs6759892	4.19×10^{-23}	2.93×10^{-22}	0.1158	0.0113	7.87×10^{-22}	5.51×10^{-21}	0.3458
rs2070959	1.26×10^{-24}	8.84×10^{-24}	0.1218	0.0115	3.63×10^{-23}	2.54×10^{-22}	0.3570
rs1105879	1.41×10^{-26}	9.87×10^{-26}	0.1249	0.0113	7.64×10^{-25}	5.35×10^{-24}	0.3731
rs887829	2.49×10^{-32}	1.74×10^{-31}	0.1398	0.0113	9.34×10^{-30}	6.54×10^{-29}	0.4080
rs6742078	6.39×10^{-32}	4.47×10^{-31}	0.1385	0.0112	2.06×10^{-29}	1.44×10^{-28}	0.4055

rs4148325	5.30×10^{-32}	3.71×10^{-31}	0.1388	0.0113	1.75×10^{-29}	1.22×10^{-28}	0.4058

NOTE. SE: Standard error; Bonf: Bonferroni; Corr: Correlation.

Supplementary Table S7. Variants associated at the exome-wide level with the serum conjugated bilirubin level in the Oasi cohort subjects

Marker	Regression *P*-value	Regression Bonf. *P*-value	Regression Slope	Regression Slope SE	Corr/Trend *P*-value	Corr/Trend Bonf. *P*-value	Corr/Trend R
	Initial study (n=400)						
rs2070959	4.37×10^{-8}	2.41×10^{-3}	0.0902	0.0162	7.32×10^{-8}	4.03×10^{-3}	0.2702
rs1105879	4.49×10^{-8}	2.47×10^{-3}	0.0879	0.0158	7.53×10^{-8}	4.14×10^{-3}	0.2706
rs6759892	1.33×10^{-7}	7.31×10^{-3}	0.0850	0.0158	2.06×10^{-7}	1.14×10^{-2}	0.2606
rs887829	3.36×10^{-9}	1.85×10^{-4}	0.0957	0.0158	6.81×10^{-9}	3.75×10^{-4}	0.2909
rs6742078	7.90×10^{-9}	4.35×10^{-4}	0.0930	0.0158	1.49×10^{-8}	8.23×10^{-4}	0.2838
rs4148325	7.90×10^{-9}	4.35×10^{-4}	0.0930	0.0158	1.49×10^{-8}	8.23×10^{-4}	0.2838
	***In silico* replication study (n=373)**						
rs6759892	7.26×10^{-18}	4.35×10^{-17}	0.1114	0.0123	2.14×10^{-16}	1.28×10^{-15}	0.4259
rs2070959	1.39×10^{-16}	8.36×10^{-16}	0.1087	0.0125	2.48×10^{-15}	1.49×10^{-14}	0.4103
rs1105879	2.06×10^{-18}	1.24×10^{-17}	0.1141	0.0123	8.21×10^{-17}	4.93×10^{-16}	0.4365
rs887829	6.96×10^{-22}	4.17×10^{-21}	0.1277	0.0125	1.27×10^{-19}	7.62×10^{-19}	0.4699
rs6742078	8.15×10^{-22}	4.89×10^{-21}	0.1272	0.0124	1.46×10^{-19}	8.74×10^{-19}	0.4697
rs4148325	6.96×10^{-22}	4.17×10^{-21}	0.1277	0.0125	1.27×10^{-19}	7.62×10^{-19}	0.4699
	Pooled analysis from initial and replication studies (n=773)						
rs6759892	6.51×10^{-21}	3.91×10^{-20}	0.0997	0.0103	6.98×10^{-20}	4.19×10^{-19}	0.3289
rs2070959	1.11×10^{-20}	6.63×10^{-20}	0.1010	0.0105	1.12×10^{-19}	6.72×10^{-19}	0.3271
rs1105879	1.66×10^{-21}	9.94×10^{-21}	0.1016	0.0103	2.12×10^{-20}	1.27×10^{-19}	0.3357
rs887829	3.54×10^{-25}	2.13×10^{-24}	0.1120	0.0104	1.20×10^{-23}	7.20×10^{-23}	0.3612
rs6742078	1.89×10^{-24}	1.14×10^{-23}	0.1100	0.0104	5.19×10^{-23}	3.11×10^{-22}	0.3560
rs4148325	1.60×10^{-24}	9.57×10^{-24}	0.1103	0.0104	4.45×10^{-23}	2.67×10^{-22}	0.3563

NOTE. SE: Standard error; Bonf: Bonferroni; Corr: Correlation.

Supplementary Table S8. Loci associated with total serum bilirubin level using the gene-based combined multivariate and collapsing method

Gene Name	Chr	Position, start	Position, stop	*P*-Value	R^2	Bonf. *P*-value	FDR, *P*-value	Sample Size Used	# Markers Total	# in Bin=0	# in Bin=1
UGT1A4	2	234627438	234681945	9.99×10^{-19}	0.10	1.49×10^{-14}	1.49×10^{-14}	773	33	28	5
UGT1A3	2	234637773	234681945	1.27×10^{-18}	0.10	1.88×10^{-14}	9.42×10^{-15}	773	25	20	5
UGT1A1	2	234668919	234681945	1.28×10^{-18}	0.10	1.90×10^{-14}	6.34×10^{-15}	773	15	13	2
UGT1A5	2	234621638	234681945	1.02×10^{-13}	0.07	1.52×10^{-9}	3.80×10^{-10}	773	37	31	6
UGT1A6	2	234600321	234681951	6.35×10^{-10}	0.05	9.45×10^{-6}	1.89×10^{-6}	773	43	34	9
UGT1A7	2	234590584	234681945	7.67×10^{-10}	0.05	1.14×10^{-5}	1.90×10^{-6}	773	54	45	9

NOTE. Chr: chromosome ; Bonf: Bonferroni; FDR : False Discovery Rate

Supplementary Table S9. Linkage disequilibrium pairwise analysis of the UGT1A1 locus SNPs

Marker 1	Function	HGVS	Marker 2	Function	HGVS	Distance in markers	Distance in kb	EM – D Prime
rs887829	Intronic	c.-364C>T	rs4148323	Missense	p.Gly71Arg	2	0.574	0.70
rs887829	Intronic	c.-364C>T	rs144398951	Missense	p.Ile215Val	5	1.006	1
rs887829	Intronic	c.-364C>T	rs35003977	Missense	p.Val225Gly	6	1.037	0.99
rs887829	Intronic	c.-364C>T	rs57307513	Missense	p.Ser250Pro	8	1.111	1
rs4148325	Intronic	c.865-2371C>T	rs4148323	Missense	p.Gly71Arg	8	4.165	0.69
rs4148325	Intronic	c.865-2371C>T	rs144398951	Missense	p.Ile215Val	5	3.733	1
rs4148325	Intronic	c.865-2371C>T	rs35003977	Missense	p.Val225Gly	4	3.702	0.99
rs4148325	Intronic	c.865-2371C>T	rs57307513	Missense	p.Ser250Pro	2	3.628	1
rs6742078	Intronic	c.864+2842G>T	rs4148323	Missense	p.Gly71Arg	7	3.495	0.69
rs6742078	Intronic	c.864+2842G>T	rs144398951	Missense	p.Ile215Val	4	3.063	1
rs6742078	Intronic	c.864+2842G>T	rs35003977	Missense	p.Val225Gly	3	3.032	0.99
rs6742078	Intronic	c.864+2842G>T	rs57307513	Missense	p.Ser250Pro	1	2.958	1
rs4148323	Missense	p.Gly71Arg	rs144398951	Missense	p.Ile215Val	3	0.432	1
rs4148323	Missense	p.Gly71Arg	rs57307513	Missense	p.Ser250Pro	6	0.537	1
rs4148323	Missense	p.Gly71Arg	rs35003977	Missense	p.Val225Gly	4	0.463	1
rs144398951	Missense	p.Ile215Val	rs57307513	Missense	p.Ser250Pro	3	0.105	1
rs144398951	Missense	p.Ile215Val	rs35003977	Missense	p.Val225Gly	1	0.031	1
rs35003977	Missense	p.Val225Gly	rs57307513	Missense	p.Ser250Pro	2	0.074	1

NOTE. HGVS: Human genome variation society

Supplementary Table S10. Association between the low-frequency coding variant rs35003977 (p.Val225Gly) of *UGT1A1* and serum bilirubin level beyond the upper normal limit in the allelic model

UGT1A1, exon 1 **rs35003977 (p.Val225Gly)**	***P*-value***	**Odds Ratio†**	**95%, CI**
Total bilirubin > 1.2 mg/dL	4.31×10^{-2}	4.82	1.29 to 18.11
Unconjugated bilirubin > 0.7 mg/dL	1.78×10^{-2}	4.52	1.42 to 14.38
Conjugated bilirubin > 0.3 mg/dL	3.99×10^{-2}	7.45	1.58 to 35.11

NOTE. CI: confidence interval.

* Logistic regression analysis

† Odds ratio for the minor allele

Supplementary Table S11. Genome-wide association studies that reported associations on unconjugated, conjugated, and/or total bilirubin

Author	Year	Geographical area or ethnicity	Study type	Studied phenotype	Associated phenotype	Initial study	Replication study	Total	Gene	Top SNPs	Reference
Saito A, *et al.*	2009	Japan	GWAS	Total bilirubin	None	752		752	*UGT1A1*	rs4148325 ; rs4148324 ; rs4148326 ; rs3755319 ; rs4148323	1
Sanna S, *et al.*	2009	Sardinia	GWAS	Total bilirubin	None	4300	1862	6162	*UGT1A1*	rs887829	2
									G6PD	rs766420	
									SLCO1B3	rs2117032	
Lin JP, *et al.*	2009	Framingham	GWAS	Total bilirubin	CVD	1345		1345	*UGT1A1*	rs1113193	3
Johnson AD, *et al.*	2009	Framingham Rotterdam Reykjavik	GWAS Meta-analysis (GWAS-MA)	Total bilirubin	Gallstones (no association)	9464		9464	*UGT1A1*	rs6742078 ; rs887829 ; rs4148324 ; rs4148325 (All 4 SNPs in perfect LD)	4
									SLCO1B1	rs4149056 (Val174Ala)	
Buch S, *et al.*	2010	Germany	Candidate-gene Based on GWAS-MA	Gallstone composition (Bilirubin > 5%)	Gallstone disease (gender-specific effect)	1018		1018	*UGT1A1*	rs6742078	5
									SLCO1B1	rs4149056	
Kang TW, *et al.*	2010	Korea	GWAS	Total bilirubin	None	8841	1096	9937	*UGT1A1*	rs11891311 ; rs4148323	6
									SLCO1B3	rs2417940	
Bielinski SJ, *et al.*	2011	USA	GWAS	Total bilirubin	None	6307		6307	*UGT1A1*	rs4148325	7
									SLCO1B1	rs4363657	
Datta S, *et al.*	2012	India	GWAS	Unconjugated bilirubin	Excluding *UGT1A1*	182		182	*NUP153*	rs2328136	8
Chen G, *et al.*	2012	African American	GWAS	Total bilirubin		619		619	*UGT1A1*	rs887829	9
Milton JN, *et al.*	2013	African American	GWAS	Total bilirubin	Gallstone disease in sickle cell anemia (significant association)	1117	530	1647	*UGT1A1*	rs887829	10
Dai X, *et al.*	2013	China	GWAS	Total bilirubin Unconjugated bilirubin Conjugated bilirubin	None	1452		1452	*UGT1A1*	rs6742078 ; rs4148323	11
									SLCO1B3	rs2417940 ; rs4149132	

NOTE. The underlined SNPs are GWAS-significant in at least two genome-wide association studies

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