The *UMOD* Locus Shows Evidence of Pathogen Adaptation through Human Evolution

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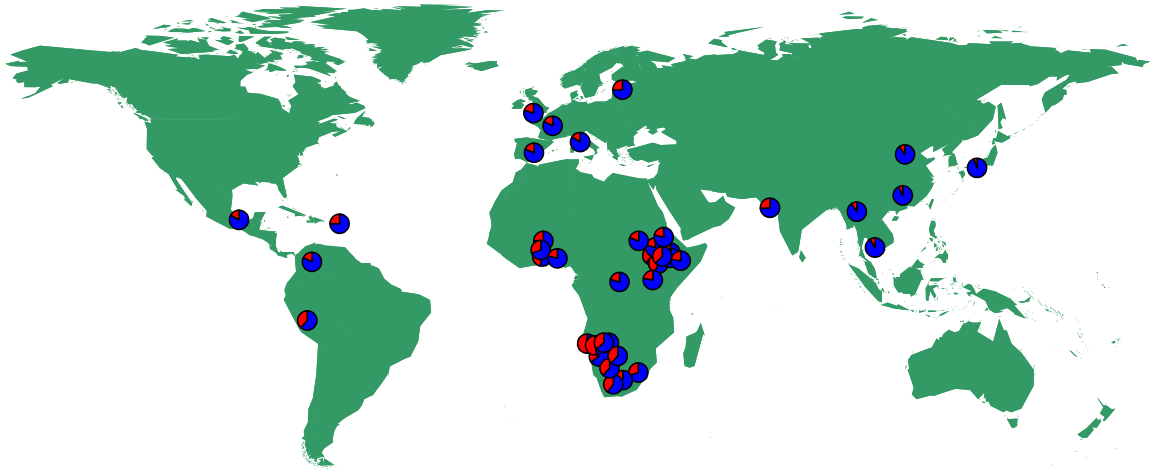
SUPPLEMENTARY MATERIAL

SUPPLEMENTAL FIGURE LEGENDS

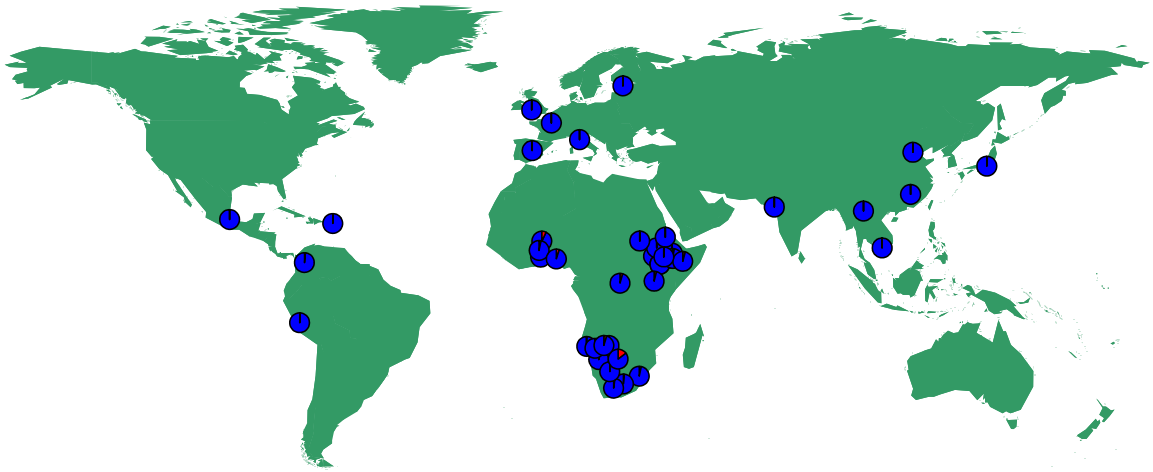
Supplemental Figure 1. Distribution of ancestral (blue) and derived (red) allele frequencies at the variants rs4293393 of the *UMOD* gene and rs75770792 (T555I) of the *CORIN* gene in 44 worldwide populations. The ancestral allele of *UMOD* is the risk one, whereas the ancestral allele of *CORIN* is the protective one.

Supplemental Figure 2. Decay of extended haplotype homozygosity (EHH) for *UMOD* variant in HapMap populations. Haplotype decay around rs4293393 in Luhya in Webuye - Kenya (LWK), Maasai in Kinyawa - Kenya (MKK), Yoruba in Ibadan - Nigeria (YRI), Utah residents with Northern and Western European ancestry (CEU) and Gujarati Indians in Houston (GIH). The ancestral allele is reported in blue, the derived allele is reported in red.

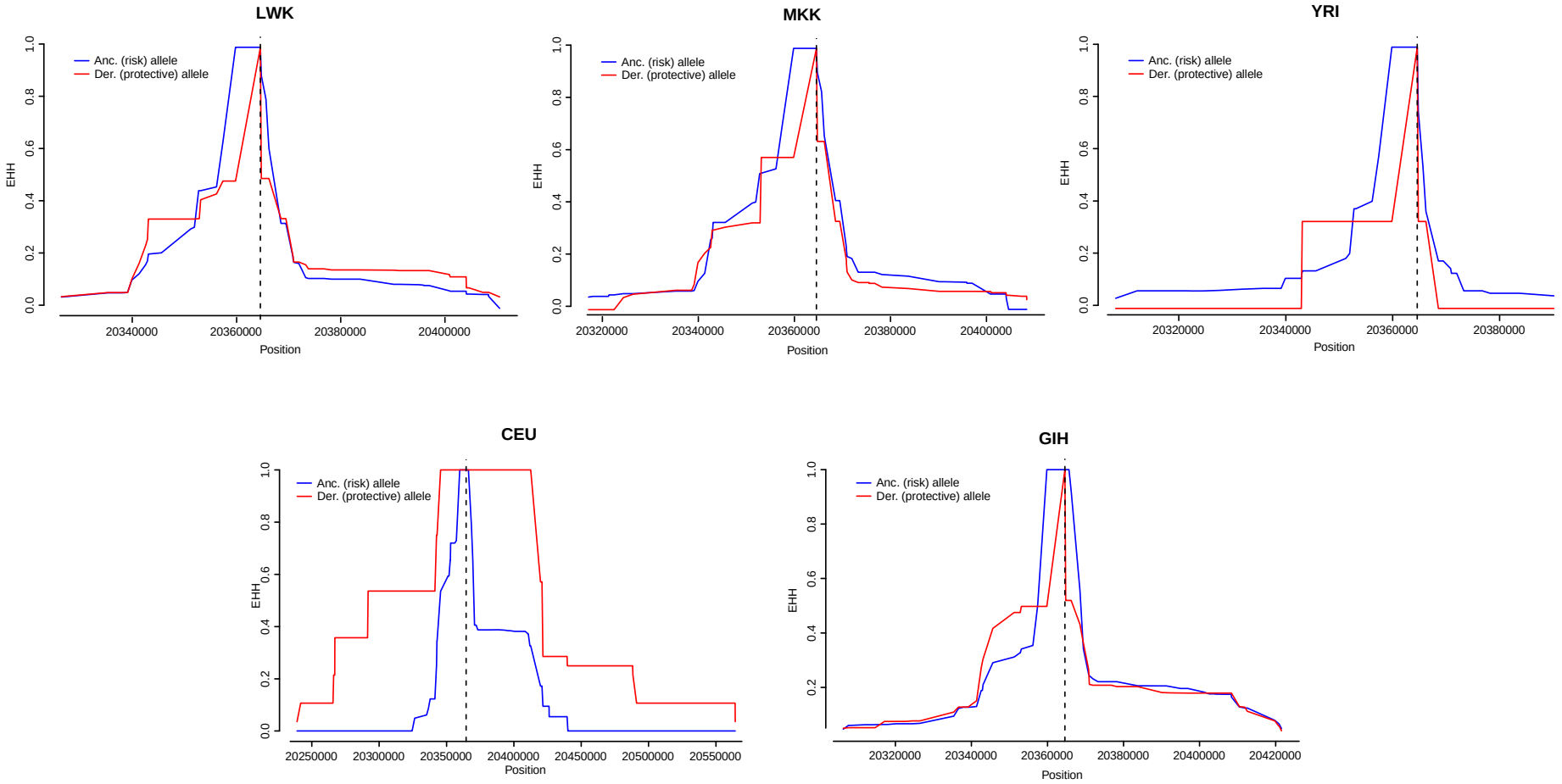
rs4293393 *UMOD*
Ancestral allele: T
Derived allele: C



rs75770792 *CORIN*
Ancestral allele: G
Derived allele: A



Supplemental Figure 1



Supplemental Figure 2

Supplemental Table 1. *UMOD* rs4293393 genotype in ancient genomes of archaic or anatomically modern humans.

Sample	Location	Coverage	Age	*UMOD* rs4293393	Reference
Mezmaiskaya-1 (Neanderthal)	Siberia	52x	60,000-70,000 ybp	C/C	[1]
Denisovan	Siberia	30x	50,000 ybp	C/C	[2]
Ust_Ishim	Siberia	42x	45,000 ybp	T/T	[3]
Anzick-1	Montana	14.4x	12,707-12,556 ybp	T/T	[4]
Motala-3	Sweden	0.55x	8,000 ybp	T/T	[5]
Motala-12	Sweden	2.4x	8,000 ybp	T/T	[5]
Mota	Ethiopian	12.5x	4,000 ybp	T/T	[6]
Paleoeskimo-Saqqaq	Greenland	20x	4,100-3,900 ybp	T/T	[7]

ybp, years before present.

Supplemental Table 2. Allelic frequencies of selected variants in worldwide populations.

				rs699 (*AGT*)			rs776746 (*CYP3A5*)			rs4293393 (*UMOD*)				
Population	N	Lat.	Long.	A1	A2	Fr(A1)	A1	A2	Fr(A1)	A1	A2	Fr(A1)	**References**	**Genotyping chip**
Abhkasians	20	42,97	41,44	T	C	0,53	G	A	0,92	C	T	0,25	[8]	Illumina_Human610_K
Adygei	17	44,81	40,21	T	C	0,53	G	A	0,88	C	T	0,24	[9]	Illumina_HumanHap650K
Afar	12	8,49	40,49	T	C	0,38	G	A	0,54	C	T	0,27	[10]	Illumina_Omni_1M_chip
African_Ancestry	83	31,72	-84,49	T	C	0,26	G	A	0,34	C	T	0,21	[11]	
Algeria	19	36,75	3,04	T	C	-	G	A	0,74	C	T	0,11	[12]	Affy_GenomeWideSNP_6.0
Altaian	16	51,79	82,68	T	C	0,22	G	A	0,91	C	T	0,16	[7,13]	Illumina_Human610_Quad_v1.0, Illumina_Human660W_Quad_v1.0
Amhara	26	7,55	40,63	T	C	0,40	G	A	0,66	C	T	0,31	[10]	Illumina_Omni_1M_chip
Anuak	23	8,24	34,59	T	C	0,17	G	A	0,24	C	T	0,39	[10]	Illumina_Omni_1M_chip
Araba	22	42,90	-2,69	T	C	0,59	G	A	-	C	T	0,20	[14]	Illumina_Human_1_100K
Ariblacksmith	17	5,78	36,57	T	C	0,47	G	A	0,50	C	T	0,47	[10]	Illumina_Omni_1M_chip
Aricultivator	24	5,78	36,57	T	C	0,22	G	A	0,29	C	T	0,43	[10]	Illumina_Omni_1M_chip
Armenian	35	40,07	45,04	T	C	0,50	G	A	0,96	C	T	0,26	[15,8]	Illumina_Human610_K, Illumina_Human610_Quad
Ashkenazy_Jewes	21	61,52	105,32	T	C	0,62	G	A	0,86	C	T	0,17	[15]	Illumina_Human610_Quad
Aussie	477	-35,3	149,13	T	C	0,58	G	A	0,92	C	T	0,17	[16]	Illumina_HumanHap300_Duo, Illumina_HumanHap_300
Balkar	19	45,11	41,37	T	C	0,50	G	A	0,84	C	T	0,26	[8]	Illumina_Human610_K
Balochi	25	27,53	60,58	T	C	0,36	G	A	0,80	C	T	0,12	[9]	Illumina_HumanHap650K
Bantu_N.E.	12	-3,37	35,68	T	C	0,13	G	A	0,17	C	T	0,04	[9]	Illumina_HumanHap650K
Bantu_S.E.	25	-23,54	29,27	T	C	0,06	G	A	0,12	C	T	0,22	[9]	Illumina_HumanHap650K
Bantu_S.W.	15	-17,98	14,25	T	C	0,20	G	A	0,27	C	T	0,23	[9]	Illumina_HumanHap650K
Bedouin	48	29,40	36,31	T	C	0,44	G	A	0,85	C	T	0,16	[9]	Illumina_HumanHap650K
Biaka_Pygmies	32	3,94	17,02	T	C	0,03	G	A	0,09	C	T	0,50	[9]	Illumina_HumanHap650K
Bizkaya	22	43,22	-2,69	T	C	0,48	G	A	-	C	T	0,16	[14]	Illumina_Human_1_100K
Brahui	25	27,86	66,12	T	C	0,46	G	A	0,88	C	T	0,16	[9]	Illumina_HumanHap650K
Bulgarian	13	42,73	25,49	T	C	0,46	G	A	0,96	C	T	0,12	[8]	Illumina_Human610_K

Burmese	15	19,00	98,00	T	C	0,27	G	A	0,77	C	T	0,20	[17]	Illumina_HumanHap_610K
Burusho	25	35,22	75,80	T	C	0,30	G	A	0,78	C	T	0,38	[9]	Illumina_HumanHap650K
Buryat	19	49,54	114,39	T	C	0,24	G	A	0,95	C	T	0,11	[7]	Illumina_Human660W_Quad_v1.0
Cambodian	11	12,57	104,99	T	C	0,18	G	A	0,73	C	T	0,09	[9]	Illumina_HumanHap650K
Canary_Island	17	28,10	-15,4	T	C	-	G	A	0,88	C	T	0,21	[18]	Affy_GenomeWideSNP_6.0
Utah	165	39,32	-111,09	T	C	0,59	G	A	0,96	C	T	0,17	[11]	
Chamar	10	27,57	80,10	T	C	0,35	G	A	0,35	C	T	0,30	[19]	Illumina_HumanHap650Yv3
Chechen	20	49,82	15,47	T	C	0,48	G	A	0,97	C	T	0,18	[8]	Illumina_Human610_K
Chinese	85	39,73	-104,98	T	C	0,19	G	A	0,76	C	T	0,05	[11]	
Chukchi	14	56,24	93,66	T	C	0,36	G	A	0,89	C	T	0,46	[7]	Illumina_Human660W_Quad_v1.0
Chuvash	17	55,56	46,93	T	C	0,56	G	A	0,97	C	T	0,15	[15]	Illumina_Human610_Quad
Colombian	13	4,57	-74,3	T	C	0,15	G	A	0,85	C	T	0,69	[9]	Illumina_HumanHap650K
Colouredcolesberg	20	-30,71	25,09	T	C	0,20	G	A	0,40	C	T	0,33	[20]	Illumina_Omni_2.5M
Colouredwellington	20	-30,71	25,09	T	C	0,20	G	A	0,65	C	T	0,33	[20]	Illumina_Omni_2.5M
Cypriots	12	35,13	33,43	T	C	0,58	G	A	0,96	C	T	0,13	[15]	Illumina_Human610_Quad
Dai	10	22,01	100,80	T	C	0,10	G	A	0,55	C	T	0,20	[9]	Illumina_HumanHap650K
Denmark	162	56,26	9,50	T	C	0,60	G	A	0,95	C	T	0,17	[21]	Illumina_HumanHap_300
Dharkar	12	27,57	80,10	T	C	0,58	G	A	0,58	C	T	0,38	[19]	Illumina_HumanHap650Yv3
Druze	47	32,45	36,80	T	C	0,44	G	A	0,91	C	T	0,14	[9]	Illumina_HumanHap650K
Dusadh	10	27,57	80,10	T	C	0,30	G	A	0,70	C	T	0,50	[19]	Illumina_HumanHap650Yv3
East_Greenlander	10	67,76	-51,65	T	C	0,45	G	A	-	C	T	0,15	[7]	Illumina_Human660W_Quad_v1.0
Egypt	31	26,82	30,80	T	C	0,25	G	A	0,87	C	T	0,21	[12,15]	Affy_GenomeWideSNP_6.0, Illumina_Human610_Quad
Esomali	17	9,15	40,49	T	C	0,30	G	A	0,47	C	T	0,23	[10]	Illumina_Omni_1M_chip
Estonians	15	58,59	25,01	T	C	0,67	G	A	0,80	C	T	0,20	[13]	Illumina_Human610_Quad_v1.0
Ethiopian_Jewes	13	9,15	40,49	T	C	0,31	G	A	0,62	C	T	0,42	[15]	Illumina_Human610_Quad
Ethiopians	19	9,15	40,49	T	C	0,34	G	A	0,68	C	T	0,34	[15]	Illumina_Human610_Quad
Evenki	16	45,74	126,66	T	C	0,28	G	A	0,87	C	T	0,19	[7]	Illumina_Human610_Quad_v1.0
Finland	157	61,92	25,75	T	C	0,58	G	A	0,95	C	T	0,19	[21]	Illumina_HumanHap300
French	29	46,23	2,21	T	C	0,69	G	A	0,91	C	T	0,24	[9]	Illumina_HumanHap650K

French_Basque	24	42,99	-2,62	T	C	0,60	G	A	0,96	C	T	0,23	[9]	Illumina_HumanHap650K
Georgians	20	42,32	43,36	T	C	0,70	G	A	0,97	C	T	0,28	[15]	Illumina_Human610_Quad
Gipuzkoa	22	43,07	-2,22	T	C	0,66	G	A	-	C	T	0,30	[14]	Illumina_Human_1_100K
Guighanakgal	15	7,94	-1,02	T	C	0,03	G	A	0,30	C	T	0,47	[20]	Illumina_Omni_2.5M
Gujarati	88	29,76	-95,36	T	C	0,39	G	A	0,76	C	T	0,28	[11]	
Gumuz	19	10,78	35,57	T	C	0,39	G	A	0,37	C	T	0,21	[10]	Illumina_Omni_1M_chip
Hadza	17	-3,37	35,68	T	C	0,04	G	A	0,25	C	T	0,15	[22]	Illumina_HumanHap550
Han	128	39,91	116,39	T	C	0,19	G	A	0,71	C	T	0,09	[9]	Illumina_HumanHap650K
Hazara	29	33,94	67,71	T	C	0,29	G	A	0,74	C	T	0,12	[9,23]	Illumina_HumanHap650K, Illumina_HumanHap650K
Hungarians	20	47,16	19,50	T	C	0,70	G	A	0,90	C	T	0,23	[15]	Illumina_Human610_Quad
Iparralde	24	43,08	-2,27	T	C	0,60	G	A	-	C	T	0,23	[14]	Illumina_Human_1_100K
Iranians	20	32,43	53,69	T	C	0,45	G	A	0,90	C	T	0,35	[15]	Illumina_Human610_Quad
Iraqi_Jewes	11	33,22	43,68	T	C	0,59	G	A	0,91	C	T	0,41	[15]	Illumina_Human610_Quad
Irish	211	53,34	-6,27	T	C	0,58	G	A	0,94	C	T	0,17	[24]	Illumina_HumanHap550
Japanese	115	36,20	138,25	T	C	0,20	G	A	0,74	C	T	0,05	[9,11]	Illumina_HumanHap650K
Jordanians	20	30,59	36,24	T	C	0,48	G	A	0,87	C	T	0,20	[15]	Illumina_Human660W_Quad_v1.0
Juhoansi	18	-19,28	13,51	T	C	0,03	G	A	0,19	C	T	0,53	[20]	Illumina_Omni_2.5M
Kalash	25	34,02	74,25	T	C	0,36	G	A	0,76	C	T	0,24	[9]	Illumina_HumanHap650K
Karitiana	24	-9,01	-65	T	C	-	G	A	0,77	C	T	0,08	[9]	Illumina_HumanHap650K
Karretjie	20	-32	21,99	T	C	0,05	G	A	0,22	C	T	0,40	[20]	Illumina_Omni_2.5M
Kazakhs	18	48,02	66,92	T	C	0,36	G	A	0,83	C	T	0,17	[13]	Illumina_Human660W_Quad_v1.0
Khwe	17	-23,15	23,41	T	C	0,06	G	A	0,12	C	T	0,38	[20]	Illumina_Omni_2.5M
Kol	17	27,19	80,33	T	C	0,38	G	A	0,74	C	T	0,32	[19]	Illumina_HumanHap650Yv3
Koryak	17	61,43	166,79	T	C	0,21	G	A	0,91	C	T	0,24	[7]	Illumina_Human660W_Quad_v1.0
Kumyk	14	42,14	47,09	T	C	0,57	G	A	0,93	C	T	0,18	[8]	Illumina_Human610_K
Kyrgyzians	19	41,20	74,76	T	C	0,34	G	A	0,95	C	T	0,29	[13]	Illumina_Human660W_Quad_v1.0
Lahu	10	101,98	24,99	T	C	0,05	G	A	0,70	C	T	0,10	[9]	Illumina_HumanHap650K
Lebanese	82	33,85	35,86	T	C	0,49	G	A	0,90	C	T	0,18	[15,25]	Illumina_Human610_Quad, Illumina HumanHap 610K
Lezgins	18	41,45	48,28	T	C	0,39	G	A	0,94	C	T	0,22	[15]	Illumina_Human610_Quad

Libya	17	26,13	17,23	T	C	-	G	A	0,76	C	T	0,15	[12]	Affy_GenomeWideSNP_6.0
Lithuanians	10	55,17	23,88	T	C	0,50	G	A	0,95	C	T	0,20	[15]	Illumina_Human610_Quad
Luhya	90	0,62	34,77	T	C	0,11	G	A	0,13	C	T	0,22	[11]	
Maasai	171	-2,81	37,92	T	C	0,14	G	A	0,49	C	T	0,29	[11]	
Makrani	25	22,26	71,19	T	C	0,40	G	A	0,86	C	T	0,28	[9]	Illumina_HumanHap650K
Mandenka	24	12,00	-12	T	C	0,04	G	A	0,31	C	T	0,10	[9]	Illumina_HumanHap650K
Maris	15	56,43	47,96	T	C	0,73	G	A	0,80	C	T	0,40	[13]	Illumina_HumanHap650Yv3
Maya	25	22,92	-102,36	T	C	0,08	G	A	0,70	C	T	0,44	[9]	Illumina_HumanHap650K
Mbuti_Pygmies	15	1,00	29,00	T	C	-	G	A	0,07	C	T	0,60	[9]	Illumina_HumanHap650K
Mexican	77	34,05	-118,24	T	C	0,31	G	A	0,74	C	T	0,19	[11]	
Miaozu	10	26,60	106,71	T	C	0,15	G	A	0,65	C	T	0,00	[9]	Illumina_HumanHap650K
Mongola	19	46,86	103,85	T	C	0,21	G	A	0,76	C	T	0,16	[7,9]	Illumina_HumanHap650K, Illumina_Human660W_Quad_v1.0
Mordovian	15	54,24	44,07	T	C	0,50	G	A	0,90	C	T	0,13	[8]	Illumina_Human610_K
Moroccan_Jewes	16	31,79	-7,09	T	C	0,59	G	A	0,87	C	T	0,34	[15]	Illumina_Human660W_Quad_v1.0
Moroccans	10	31,79	-7,09	T	C	0,35	G	A	0,75	C	T	0,15	[15]	Illumina_Human660W_Quad_v1.0
Morocco_N	18	33,07	-4,71	T	C	-	G	A	0,83	C	T	0,17	[12]	Affy_GenomeWideSNP_6.0
Morocco_S	16	23,36	-14,35	T	C	-	G	A	0,62	C	T	0,16	[12]	Affy_GenomeWideSNP_6.0
Mozabite	30	31,95	4,06	T	C	0,50	G	A	0,85	C	T	0,25	[9]	Illumina_HumanHap650K
Nafarroa	17	42,69	-1,67	T	C	0,68	G	A	-	C	T	0,24	[14]	Illumina_Human_1_100K
Nama	20	-19,83	16,09	T	C	0,05	G	A	0,32	C	T	0,53	[20]	Illumina_Omni_2.5M
NAN_Melanesian	19	-0,79	113,92	T	C	0,03	G	A	0,82	C	T	0,45	[9]	Illumina_HumanHap650K
Netherlands	290	52,13	5,29	T	C	0,63	G	A	0,94	C	T	0,17	[16]	Illumina_HumanHap300_Duo
Nganassan	15	74,12	96,46	T	C	0,30	G	A	0,90	C	T	0,00	[7]	Illumina_Human660W_Quad_v1.0
Nogai	16	44,49	45,74	T	C	0,56	G	A	0,84	C	T	0,22	[8]	Illumina_Human610_K
North_Italian	13	41,87	12,59	T	C	0,38	G	A	0,81	C	T	0,04	[9]	Illumina_HumanHap650K
North_Ossetian	15	42,38	44,05	T	C	0,53	G	A	0,90	C	T	0,20	[8]	Illumina_Human610_K
Orcadian	16	59,04	-3,15	T	C	0,56	G	A	0,84	C	T	0,13	[9]	Illumina_HumanHap650K
Oromo	21	7,55	40,63	T	C	0,43	G	A	0,57	C	T	0,24	[10]	Illumina_Omni_1M_chip
Oroqen	10	126,56	48,75	T	C	0,10	G	A	0,85	C	T	0,00	[9]	Illumina_HumanHap650K
Palestinian	51	31,95	35,23	T	C	0,48	G	A	0,82	C	T	0,20	[9]	Illumina_HumanHap650K

Papuan	17	-4,27	138,08	T	C	0,09	G	A	0,79	C	T	0,09	[9]	Illumina_HumanHap650K
Pathan	23	17,05	80,10	T	C	0,46	G	A	0,87	C	T	0,17	[9]	Illumina_HumanHap650K
Pima	25	29,05	-108,02	T	C	0,10	G	A	0,46	C	T	0,04	[9]	Illumina_HumanHap650K
Romanians	16	45,15	24,95	T	C	0,38	G	A	1,00	C	T	0,13	[15]	Illumina_Human610_Quad
Russian	28	61,52	105,32	T	C	0,57	G	A	0,93	C	T	0,23	[13,15,9]	Illumina_HumanHap650K, Ilumina_HumanHap650Y , Illumina Human610-Quad v1.0
Sahara_OCC	18	23,98	-12,99	T	C	-	G	A	0,79	C	T	0,08	[12]	Affy_GenomeWideSNP_6.0
San	76	-23,54	30,80	T	C	0,13	G	A	0,31	C	T	0,36	[9]	Illumina_HumanHap650K
Sandawe	28	-11,77	33,99	T	C	0,11	G	A	0,21	C	T	0,30	[22]	Illumina_HumanHap550
Sardinian	28	40,12	9,01	T	C	0,63	G	A	0,96	C	T	0,21	[9]	Illumina_HumanHap650K
Saudis	20	23,89	45,08	T	C	0,55	G	A	0,92	C	T	0,15	[15]	Illumina_Human660W_Quad_v1.0
Selkup	17	61,01	99,19	T	C	0,29	G	A	0,74	C	T	0,00	[7,13]	Illumina_Human610_Quad_v1.0, Illumina Human660W-Quad v1.0
Sephardic_Jewes	19	38,73	37,06	T	C	0,53	G	A	0,97	C	T	0,13	[15]	Illumina_Human610_Quad
She	10	26,10	119,30	T	C	0,20	G	A	0,55	C	T	0,05	[9]	Illumina_HumanHap650K
Sindhi	25	35,57	72,42	T	C	0,30	G	A	0,78	C	T	0,28	[9]	Illumina_HumanHap650K
Somali	23	6,66	43,79	T	C	0,25	G	A	0,46	C	T	0,23	[10]	Illumina_Omni_1M_chip
Basque	20	42,74	-1,99	T	C	-	G	A	0,95	C	T	0,30	[12]	Affy_GenomeWideSNP_6.0
Spaniards	12	40,46	-3,74	T	C	0,58	G	A	0,92	C	T	0,25	[15]	Illumina_Human610_Quad
Spain_NW	17	42,50	-8,1	T	C	-	G	A	0,94	C	T	0,13	[18]	Affy_GenomeWideSNP_6.0
Spain_S	17	37,45	-5,98	T	C	-	G	A	1,00	C	T	0,21	[18]	Affy_GenomeWideSNP_6.0
Sudanese	24	12,86	30,22	T	C	0,11	G	A	0,15	C	T	0,20	[10]	Illumina_Omni_1M_chip
Surui	21	-60,88	-9,99	T	C	1,00	G	A	0,83	C	T	0,21	[9]	Illumina_HumanHap650K
Sweden	302	60,13	18,64	T	C	0,57	G	A	0,92	C	T	0,20	[21]	Illumina_HumanHap300
Syrians	16	34,80	39,00	T	C	0,44	G	A	0,94	C	T	0,19	[15]	Illumina_Human660W_Quad_v1.0
Tadjik	20	38,86	71,27	T	C	0,50	G	A	0,90	C	T	0,10	[23]	Illumina_HumanHap650K
Tu	10	41,77	98,01	T	C	0,20	G	A	0,90	C	T	0,05	[9]	Illumina_HumanHap650K
Tujia	10	28,31	109,74	T	C	0,15	G	A	0,50	C	T	0,05	[9]	Illumina_HumanHap650K
Tunisia	18	33,89	9,54	T	C	-	G	A	0,86	C	T	0,11	[12]	Affy_GenomeWideSNP_6.0
Turkmen	19	38,97	59,57	T	C	0,47	G	A	0,89	C	T	0,21	[8,23]	Illumina_HumanHap650K,

													Illumina_Human610 K
Turks	19	38,06	35,01	T	C	0,39	G	A	0,89	C	T	0,18	[15] Illumina_Human610_Quad
Tuscan	96	43,77	11,25	T	C	0,55	G	A	0,95	C	T	0,16	[9] Illumina_HumanHap650K
Tuvinian	16	51,89	95,63	T	C	0,22	G	A	0,84	C	T	0,09	[7] Illumina_Human610_Quad_v1.0
Tygray	21	14,03	38,29	T	C	0,40	G	A	0,62	C	T	0,21	[10] Illumina_Omni_1M_chip
Ukranian	20	48,38	31,17	T	C	0,55	G	A	1,00	C	T	0,10	[8] Illumina_Human610_K
United_Kingdom	463	55,38	-3,44	T	C	0,60	G	A	0,92	C	T	0,18	[16] Illumina_HumanHap300_Duo
Uygar	10	43,79	87,63	T	C	0,55	G	A	0,95	C	T	0,20	[9] Illumina_HumanHap650K
Uzbeks	24	41,38	64,59	T	C	0,40	G	A	0,85	C	T	0,27	[15,23,13] Illumina Human660W-Quad, Illumina_HumanHap650K, Illumina Human660W-Quad v1.0
Velama	10	17,05	80,10	T	C	0,40	G	A	0,55	C	T	0,40	[19] Illumina_Human610_Quad_v1.0
West_Greenlander	10	74,75	-22,21	T	C	0,35	G	A	0,95	C	T	0,35	[7] Illumina_Human660W_Quad_v1.0
Xun	19	-23,83	22,32	T	C	0,03	G	A	0,21	C	T	0,37	[20] Illumina_Omni_2.5M
Yakut	25	65,09	135,13	T	C	0,40	G	A	0,90	C	T	0,06	[9] Illumina_HumanHap650K
Yemenese	10	15,55	48,52	T	C	0,40	G	A	0,75	C	T	0,20	[15] Illumina_Human610_Quad
Yemenite_Jewes	15	15,55	48,52	T	C	0,60	G	A	1,00	C	T	0,27	[15] Illumina_Human610_Quad
Yizu	10	27,00	104,85	T	C	0,20	G	A	0,80	C	T	0,10	[9] Illumina_HumanHap650K
Yoruba	191	7,38	3,90	T	C	0,08	G	A	0,14	C	T	0,23	[9] Illumina_HumanHap650K

Supplemental Table 3. Allelic frequencies of selected variants in worldwide populations.

				rs75770792 (*CORIN*)			rs4293393 (*UMOD*)				
Population	N	Lat	Long	A1	A2	Fr(A1)	A1	A2	Fr(A2)	**References**	**Genotyping chip**
African Caribbeans in Barbados	102	13,19	-59,54	A	G	0,07	C	T	0,76	[26]	Illumina Omni 2.5M Chip
Americans of African Ancestry in SW USA	104	35,49	-118,63	A	G	0,04	C	T	0,79	[26]	Illumina Omni 2.5M Chip
British in England and Scotland	104	54,21	-2,00	A	G	0,00	C	T	0,80	[26]	Illumina Omni 2.5M Chip
Chinese Dai in Xishuangbanna China	100	22,01	100,80	A	G	0,00	C	T	0,91	[26]	Illumina Omni 2.5M Chip
Colombians from Medellin Colombia	107	6,23	-75,59	A	G	0,02	C	T	0,83	[26]	Illumina Omni 2.5M Chip
Finnish in Finland	100	61,92	25,75	A	G	0,00	C	T	0,74	[26]	Illumina Omni 2.5M Chip
Gujarati Indian from Houston Texas	113	29,76	-95,37	A	G	0,00	C	T	0,74	[26]	Illumina Omni 2.5M Chip
Han Chinese in Bejing China	108	39,90	116,41	A	G	0,00	C	T	0,90	[26]	Illumina Omni 2.5M Chip
Iberian population in Spain	150	40,46	-3,75	A	G	0,00	C	T	0,81	[26]	Illumina Omni 2.5M Chip
Japanese in Tokyo Japan	105	35,79	139,69	A	G	0,00	C	T	0,95	[26]	Illumina Omni 2.5M Chip
Kinh in Ho Chi Minh City Vietnam	121	10,82	106,63	A	G	0,00	C	T	0,91	[26]	Illumina Omni 2.5M Chip
Luhya in Webuye Kenya	116	0,62	34,77	A	G	0,04	C	T	0,78	[26]	Illumina Omni 2.5M Chip
Mexican Ancestry from Los Angeles USA	103	34,05	-118,24	A	G	0,00	C	T	0,83	[26]	Illumina Omni 2.5M Chip
Peruvians from Lima Peru	105	-12,05	-77,04	A	G	0,00	C	T	0,62	[26]	Illumina Omni 2.5M Chip
Puerto Ricans from Puerto Rico	111	18,22	-66,59	A	G	0,00	C	T	0,75	[26]	Illumina Omni 2.5M Chip
Southern Han Chinese	153	27,50	112,46	A	G	0,00	C	T	0,93	[26]	Illumina Omni 2.5M Chip
Toscani in Italia	112	43,14	11,15	A	G	0,00	C	T	0,84	[26]	Illumina Omni 2.5M Chip
Utah Residents with Northern and Western European ancestry	183	39,32	-111,09	A	G	0,00	C	T	0,82	[26]	Illumina Omni 2.5M Chip
Yoruba in Ibadan Nigeria	189	7,40	3,92	A	G	0,05	C	T	0,79	[26]	Illumina Omni 2.5M Chip
Afar	12	8,49	40,49	A	G	0,00	C	T	0,73	[10]	Illumina Omni 1M Chip
Amhara	26	7,55	40,63	A	G	0,00	C	T	0,69	[10]	Illumina Omni 1M Chip
Anuak	23	8,24	34,59	A	G	0,00	C	T	0,61	[10]	Illumina Omni 1M Chip
Ari Blacksmith	17	5,78	36,57	A	G	0,00	C	T	0,53	[10]	Illumina Omni 1M Chip
Ari Cultivator	24	5,78	36,57	A	G	0,00	C	T	0,57	[10]	Illumina Omni 1M Chip
Ethiopian Somali	17	9,15	40,49	A	G	0,00	C	T	0,77	[10]	Illumina Omni 1M Chip

Gumuz	19	10,78	35,57	A	G	0,00	C	T	0,79	[10]	Illumina Omni 1M Chip
Maasai in Kinyawa	31	10,00	-1,50	A	G	0,03	C	T	0,69	[10]	Illumina Omni 1M Chip
Oromo	21	7,55	40,63	A	G	0,02	C	T	0,76	[10]	Illumina Omni 1M Chip
Somali	23	6,66	43,79	A	G	0,04	C	T	0,77	[10]	Illumina Omni 1M Chip
South Sudanese	24	12,86	30,22	A	G	0,00	C	T	0,80	[10]	Illumina Omni 1M Chip
Tygray	21	14,03	38,29	A	G	0,00	C	T	0,79	[10]	Illumina Omni 1M Chip
Wolayta	8	8,00	37,84	A	G	0,00	C	T	0,63	[10]	Illumina Omni 1M Chip
amaXhosa	15	-28,34	30,08	A	G	0,03	C	T	0,70	[27]	Illumina Omni 1M Chip
Basters	30	-23,28	17,29	A	G	0,00	C	T	0,65	[27]	Illumina Omni 1M Chip
Coloured	65	-30,71	25,09	A	G	0,02	C	T	0,71	[27]	Illumina Omni 1M Chip
Ju/'hoan	19	-19,02	20,54	A	G	0,00	C	T	0,50	[27]	Illumina Omni 1M Chip
Xun	33	-18,98	18,92	A	G	0,05	C	T	0,64	[27]	Illumina Omni 1M Chip
Bantu_Speakers_(Zulu,Sotho,Tswana)	32	-30,69	23,14	A	G	0,00	C	T	0,80	[20]	Illumina Omni 2.5M Chip
Gui_and_Ghana	15	7,94	-1,02	A	G	0,00	C	T	0,53	[20]	Illumina Omni 2.5M Chip
Juhoansi	18	-19,28	13,51	A	G	0,00	C	T	0,47	[20]	Illumina Omni 2.5M Chip
Karretjie	20	-32,00	21,99	A	G	0,03	C	T	0,60	[20]	Illumina Omni 2.5M Chip
Khomani	39	-26,98	20,78	A	G	0,03	C	T	0,62	[20]	Illumina Omni 2.5M Chip
Khwe	17	-23,15	23,41	A	G	0,15	C	T	0,62	[20]	Illumina Omni 2.5M Chip
Nama	20	-19,83	16,09	A	G	0,03	C	T	0,48	[20]	Illumina Omni 2.5M Chip

Supplemental Table 4. Allelic frequencies of *UMOD* rs4293393 variant and prevalence of antibiotic-resistant UTIs in worldwide populations.

Population	Country	N	Lat	Long	rs4293393 (*UMOD*) A1	A2	Fr(A1)	Gram-neg. bacteria fluoroquinolone resistant (%)	Enterobacteriaceae cephalosporin resistant (%)	*E. coli* (%)
Afar	Ethiopia	12	8,49	40,49	C	T	0,27	3,70	3,70	76,00
African_Ancestry	United States of America	83	31,72	-84,49	C	T	0,21	15,91	4,33	83,52
Amhara	Ethiopia	26	7,55	40,63	C	T	0,31	3,70	3,70	76,00
Anuak	Ethiopia	23	8,24	34,59	C	T	0,39	3,70	3,70	76,00
Araba	Spain	22	42,90	-2,69	C	T	0,20	34,90	14,60	89,74
Ariblacksmith	Ethiopia	17	5,78	36,57	C	T	0,47	3,70	3,70	76,00
Aricultivator	Ethiopia	24	5,78	36,57	C	T	0,43	3,70	3,70	76,00
Aussie	Australia	477	-35,3	149,13	C	T	0,17	11,50	7,83	100,00
Balochi	Iran	25	27,53	60,58	C	T	0,12	19,17	29,65	77,23
Biaka_Pygmies	Central African Republic	32	3,94	17,02	C	T	0,50	30,00	12,80	83,61
Bizkaya	Spain	22	43,22	-2,69	C	T	0,16	34,90	14,60	89,74
Brahui	Pakistan	25	27,86	66,12	C	T	0,16	45,40	33,80	32,07
Bulgarian	Bulgaria	13	42,73	25,49	C	T	0,12	37,40	58,30	46,25
Burmese	Thailand	15	19,00	98,00	C	T	0,20	59,60	46,70	74,12
Burusho	Pakistan	25	35,22	75,80	C	T	0,38	45,40	33,80	32,07
Utah	United States of America	165	39,32	-111,09	C	T	0,17	15,91	4,33	83,52
Chamar	India	10	27,57	80,10	C	T	0,30	63,30	54,38	71,89
Chechen	Czech Republic	20	49,82	15,47	C	T	0,18	20,80	27,50	68,91
Chinese	United States of America	85	39,73	-104,98	C	T	0,05	15,91	4,33	83,52
Cypriots	Cyprus	12	35,13	33,43	C	T	0,13	51,90	35,60	58,79
Dai	China	10	22,01	100,80	C	T	0,20	69,35	51,85	92,94
Denmark	Denmark	162	56,26	9,50	C	T	0,17	12,40	8,40	77,65
Dharkar	India	12	27,57	80,10	C	T	0,38	63,30	54,38	71,89
Druze	Syria	47	32,45	36,80	C	T	0,14	28,00	51,00	100,00
Dusadh	India	10	27,57	80,10	C	T	0,50	63,30	54,38	71,89

Esomali	Ethiopia	17	9,15	40,49	C	T	0,23	3,70	3,70	76,00
Estonians	Estonia	15	58,59	25,01	C	T	0,20	11,80	11,40	80,98
Ethiopian_Jewes	Ethiopia	13	9,15	40,49	C	T	0,42	3,70	3,70	76,00
Ethiopians	Ethiopia	19	9,15	40,49	C	T	0,34	3,70	3,70	76,00
Evenki	China	16	45,74	126,66	C	T	0,19	69,35	51,85	92,94
Finland	Finland	157	61,92	25,75	C	T	0,19	13,20	6,40	86,21
French	France	29	46,23	2,21	C	T	0,24	16,70	12,90	83,16
French_Basque	Spain	24	42,99	-2,62	C	T	0,23	34,90	14,60	89,74
Gipuzkoa	Spain	22	43,07	-2,22	C	T	0,30	34,90	14,60	89,74
Gujarati	United States of America	88	29,76	-95,36	C	T	0,28	15,91	4,33	83,52
Gumuz	Ethiopia	19	10,78	35,57	C	T	0,21	3,70	3,70	76,00
Han	China	128	39,91	116,39	C	T	0,09	69,35	51,85	92,94
Hungarians	Hungary	20	47,16	19,50	C	T	0,23	30,20	25,30	68,71
Iparralde	Spain	24	43,08	-2,27	C	T	0,23	34,90	14,60	89,74
Iranians	Iran	20	32,43	53,69	C	T	0,35	19,17	29,65	77,23
Irish	Ireland	211	53,34	-6,27	C	T	0,17	24,20	11,70	87,30
Japanese	Japan	115	36,20	138,25	C	T	0,05	30,32	21,35	81,12
Kalash	India	25	34,02	74,25	C	T	0,24	63,30	54,38	71,89
Karitiana	Brazil	24	-9,01	-65	C	T	0,08	9,00	3,45	77,52
Kazakhs	Kazakhstan	18	48,02	66,92	C	T	0,17	18,60	18,60	100,00
Khwe	Botswana	17	-23,15	23,41	C	T	0,38	11,00	NA	74,96
Kol	India	17	27,19	80,33	C	T	0,32	63,30	54,38	71,89
Lahu	China	10	101,98	24,99	C	T	0,10	69,35	51,85	92,94
Lebanese	Lebanon	82	33,85	35,86	C	T	0,18	29,00	NA	100,00
Libya	Libya	17	26,13	17,23	C	T	0,15	25,60	14,60	39,50
Lithuanians	Lithuania	10	55,17	23,88	C	T	0,20	16,00	17,40	73,38
Luhya	Kenya	90	0,62	34,77	C	T	0,22	6,50	2,20	71,88
Maasai	Kenya	171	-2,81	37,92	C	T	0,29	6,50	2,20	71,88
Makrani	India	25	22,26	71,19	C	T	0,28	63,30	54,38	71,89

Maya	Mexico	25	22,92	-102,36	C	T	0,44	55,50	10,20	100,00
Mexican	United States of America	77	34,05	-118,24	C	T	0,19	15,91	4,33	83,52
Miaozu	China	10	26,60	106,71	C	T	0.00	69,35	51,85	92,94
Moroccan_Jewes	Morocco	16	31,79	-7,09	C	T	0,34	77,70	5,60	83,51
Moroccans	Morocco	10	31,79	-7,09	C	T	0,15	77,70	5,60	83,51
Morocco_N	Morocco	18	33,07	-4,71	C	T	0,17	77,70	5,60	83,51
Morocco_S	Morocco	16	23,36	-14,35	C	T	0,16	77,70	5,60	83,51
Nafarroa	Spain	17	42,69	-1,67	C	T	0,24	34,90	14,60	89,74
Netherlands	Netherlands	290	52,13	5,29	C	T	0,17	10,70	5,50	86,92
North_Italian	Italy	13	41,87	12,59	C	T	0,04	42,80	17,38	56,31
Orcadian	United Kingdom	16	59,04	-3,15	C	T	0,13	18,65	17,30	83,52
Oromo	Ethiopia	21	7,55	40,63	C	T	0,24	3,70	3,70	76,00
Oroqen	China	10	126,56	48,75	C	T	0.00	69,35	51,85	92,94
Palestinian	West Bank	51	31,95	35,23	C	T	0,20	36,60	41,05	100,00
Pathan	India	23	17,05	80,10	C	T	0,17	63,30	54,38	71,89
Pima	Mexico	25	29,05	-108,02	C	T	0,04	55,50	10,20	100,00
Romanians	Romania	16	45,15	24,95	C	T	0,13	31,00	44,20	51,69
Sardinian	Italy	28	40,12	9,01	C	T	0,21	42,80	17,38	56,31
Saudis	Saudi Arabia	20	23,89	45,08	C	T	0,15	24,80	19,90	86,18
Sephardic_Jewes	Turkey	19	38,73	37,06	C	T	0,13	26,94	27,80	94,12
She	China	10	26,10	119,30	C	T	0,05	69,35	51,85	92,94
Sindhi	Pakistan	25	35,57	72,42	C	T	0,28	45,40	33,80	32,07
Somali	Ethiopia	23	6,66	43,79	C	T	0,23	3,70	3,70	76,00
Basque	Spain	20	42,74	-1,99	C	T	0,30	34,90	14,60	89,74
Spaniards	Spain	12	40,46	-3,74	C	T	0,25	34,90	14,60	89,74
Spain_NW	Spain	17	42,50	-8,1	C	T	0,13	34,90	14,60	89,74
Spain_S	Spain	17	37,45	-5,98	C	T	0,21	34,90	14,60	89,74
Surui	Brazil	21	-60,88	-9,99	C	T	0,21	9,00	3,45	77,52
Sweden	Sweden	302	60,13	18,64	C	T	0,20	9,65	3,15	84,90

Syrians	Syria	16	34,80	39,00	C	T	0,19	28,00	51,00	100,00
Tu	China	10	41,77	98,01	C	T	0,05	69,35	51,85	92,94
Tujia	China	10	28,31	109,74	C	T	0,05	69,35	51,85	92,94
Tunisia	Tunisia	18	33,89	9,54	C	T	0,11	50,60	17,10	100,00
Turks	Turkey	19	38,06	35,01	C	T	0,18	26,94	27,80	94,12
Tuscan	Italy	96	43,77	11,25	C	T	0,16	42,80	17,38	56,31
Tygray	Ethiopia	21	14,03	38,29	C	T	0,21	3,70	3,70	76,00
United_Kingdom	United Kingdom	463	55,38	-3,44	C	T	0,18	18,65	17,30	83,82
Uygar	China	10	43,79	87,63	C	T	0,20	69,35	51,85	92,94
Velama	India	10	17,05	80,10	C	T	0,40	63,30	54,38	71,89
Xun	Botswana	19	-23,83	22,32	C	T	0,37	11,00	NA	74,96
Yizu	China	10	27,00	104,85	C	T	0,10	69,35	51,85	92,94
Yoruba	Nigeria	191	7,38	3,90	C	T	0,23	47,80	NA	52,17

Drug-resistant UTI and *E. Coli* prevalence data were derived from Zowawi et al.[28] NA, data not available.

Supplemental Table 5. Association of ultrasensitive C-reactive protein by quintiles of urinary uromodulin-to-creatinine ratio in the CoLaus cohort (N=5,447), by sex and menopausal status.

Model	Right-censored observations, n	Q1	Q2	Q3	Q4	Q5	P LRT	P trend*
Men, n=2,585		517	517	517	517	517		
Mean uromodulin-to-creatinine ratio (mg/g) in each quintile		4.90	10.9	15.9	22.4	38.7		
Mean frequency of rs12917707 T/G allele carrier status		38.4/61.6%	37.7/62.3%	38.1/61.9%	30.6/69.4%	21.3/78.7%		<0.001
Unadjusted	33	ref	–0.04 (0.07)	–0.09 (0.07)	–0.08 (0.07)	0.02 (0.07)	0.36	0.99
Age adjusted	33	ref	–0.06 (0.07)	–0.12 (0.07)	–0.10 (0.07)	0.02 (0.07)	0.33	0.57
Fully adjusted[&]	33	ref	–0.03 (0.07)	–0.06 (0.07)	–0.03 (0.07)	0.03 (0.07)	0.60	0.65
Premenopausal women, n=1,260		252	252	252	252	252		
Mean uromodulin-to-creatinine ratio (mg/g) in each quintile		5.83	13.6	19.3	26.7	45.7		
Mean frequency of rs12917707 T/G allele carrier status		36.8/63.2%	40.6/59.4%	35.0/65.0%	25.3/74.7%	19.2/80.8%		<0.001
Unadjusted	15	ref	–0.26 (0.10)	–0.34 (0.10)	–0.34 (0.10)	–0.35 (0.10)	0.003	0.001
Age adjusted	15	ref	–0.26 (0.10)	–0.34 (0.10)	–0.34 (0.10)	–0.36 (0.10)	0.003	0.001
Fully adjusted[&]	15	ref	–0.21 (0.10)	–0.35 (0.10)	–0.29 (0.10)	–0.30 (0.10)	0.001	0.001
Postmenopausal women, n=1,602		321	320	321	320	320		

Mean uromodulin-to-creatinine ratio (mg/g) in each quintile		6.45	14.8	21.8	29.9	49.7		
Mean frequency of rs12917707 T/G allele carrier status		38.2/61.8%	40.7/59.3%	36.5/63.5%	30.3/69.7%	19.7/80.3%		<0.001
Unadjusted	27	ref	0.002	–0.14	–0.13	–0.18	0.09	0.009
			(0.09)	(0.09)	(0.09)	(0.09)		
Age adjusted	27	ref	–0.01	–0.14	–0.14	–0.18	0.09	0.009
			(0.09)	(0.09)	(0.09)	(0.09)		
Fully adjusted[&]	27	ref	0.09	–0.05	–0.04	–0.06	0.20	0.12
			(0.09)	(0.09)	(0.09)	(0.09)		

Data are coefficient (SE) from multiple tobit regression for log-transformed ultrasensitive C-reactive protein as the dependent variable.

The G allele of *UMOD* variant rs12917707 has been consistently associated with higher urinary uromodulin levels in an additive manner.[29] The rs12917707 variant is in almost complete linkage disequilibrium with the variant rs4293393 ($R^2 = 0.95$, D' = 1).

Q1, Q2, Q3, Q4, Q5: quintiles of circulating usCRP generated separately in men, pre-menopausal and post-menopausal women.

P LRT, P value from a likelihood ratio test including 4 dummy variables to test the effect of all quintiles.

P value for sex by uromodulin-to-creatinine ratio interaction = 0.025 in a model including men and women. P value for menopausal status by uromodulin-to-creatinine ratio interaction = 0.056 in a model including women only. To test for interaction, we used the continuous square-root transformed urinary uromodulin-to-creatinine ratio variable.

[&] The fully adjusted model includes age, bmi, smoking, alcohol consumption, CKD-EPI, HDL-cholesterol, log-triglyceride, lipid lowering drug, type 2 diabetes and hypertension as covariates.

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