Genetic and Clinical Factors Associated with Opioid Response in Chinese Han Patients with Cancer Pain: an exploratory cross-sectional study

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Supplementary Table 1 Characteristics and annotation of all genotyped SNPs

SNPs	Chr	Chromosome position	Genes	Localization	Minor allele	Major allele	MAF in development sample	MAF in validation sample	Gene function
rs3845446	1	181766437	CACNA1E	Intron	C	T	0.277	0.299	R-type ('high-voltage activated') calcium channel subunit
rs2995082	1	167406245	CD247	Intron	C	T	0.329	0.326	transmembrane signaling adaptor protein
rs2234918	1	29189597	OPRD1	Exon	C	T	0.203	0.219	Opioid receptors
rs2236857	1	29161609	OPRD1	Intron	C	T	0.105	0.086	Opioid receptors
rs419335	1	29151844	OPRD1	Intron	G	A	0.191	0.175	Opioid receptors
rs529520	1	29174946	OPRD1	Intron	A	C	0.138	0.121	Opioid receptors
rs581111	1	29175373	OPRD1	Intron	A	G	0.075	0.081	Opioid receptors
rs1042114	1	28812463	OPRD1	Intron	G	C, T	NA	NA	Opioid receptors
rs533123	1	28814643	OPRD1	Intron	G	A, C	NA	NA	Opioid receptors
rs5275	1	186643058	PTGS2	3'-UTR	G	A	0.177	0.188	mediates the formation of prostaglandins
rs5277	1	186648197	PTGS2	5' near gene	G	C	0.057	0.051	mediates the formation of prostaglandins
rs1061622	1	12192898	TNFRSF1B	Intron	T	G	NA	NA	tumor necrosis factor receptor

rs2952768	2	208494234	CREB1	/	C	T	0.423	0.439	induces transcription of genes in response to hormonal stimulation of the cAMP pathway
rs1143634	2	113590390	IL1B	Exon	A	G	0.021	0.019	cytokine produced by activated machrophages and involved in the inflammatory response
rs1143627	2	113594387	IL1B	5'-UTR	G	A	0.476	0.481	cytokine produced by activated machrophages and involved in the inflammatory response
rs2110726	2	102794282	IL1R1	3' near gene	A	G	0.386	0.362	cytokine receptor for interleukin 1
rs7574878	2	155607148	KCNJ3	3' near gene	G	T	0.471	0.465	GPCR-regulated potassium channel GIRK1
rs6853	3	38184370	MYD88	3'-UTR	G	A	0.014	0.017	inhibits the activity of NF-Kappa-B complexes
rs3732765	3	151090424	P2RY12	3' near gene	A	G	0.139	0.154	G-protein coupled receptor
rs9859538	3	151090963	P2RY12	3' near gene	A	G	0.144	0.161	G-protein coupled receptor
rs12645107	4	69988999	UGT2B7	/	A	G	0.365	0.406	induces transcription of genes in response to hormonal stimulation of the cAMP pathway
rs4073	4	74606024	CXCL8	5' near gene	A	T	0.402	0.405	a major mediator of the inflammatory response
rs2069762	4	123377980	IL2	5' near gene	C	A	0.335	0.314	cytokine involved in inflammatory response
rs6845322	4	157884105	PDGFC	Intron	G	A	0.433	0.439	catalytic receptors that have intracellular tyrosine kinase activity

rs10028494	4	69970937	UGT2B7	Intron	C	A	0.250	0.234	conjugation of potentially toxic xenobiotics and endogenous compounds including estrogens
rs11931604	4	69928547	UGT2B7	5' near gene	C	T	0.038	0.023	conjugation of potentially toxic xenobiotics and endogenous compounds including estrogens
rs4235108	4	69893854	UGT2B7	/	A	G	0.451	0.418	conjugation of potentially toxic xenobiotics and endogenous compounds including estrogens
rs4296738	4	69893704	UGT2B7	/	A	G	0.175	0.170	conjugation of potentially toxic xenobiotics and endogenous compounds including estrogens
rs6851533	4	69978750	UGT2B7	3' near gene	T	C	0.337	0.323	conjugation of potentially toxic xenobiotics and endogenous compounds including estrogens
rs7438135	4	69961339	UGT2B7	Intron	G	A	0.336	0.329	conjugation of potentially toxic xenobiotics and endogenous compounds including estrogens
rs7439366	4	69964338	UGT2B7	Exon	T	C	0.334	0.329	conjugation of potentially toxic xenobiotics and endogenous compounds including estrogens
rs7668282	4	69962114	UGT2B7	Intron	C	T	0.078	0.072	conjugation of potentially toxic xenobiotics and endogenous compounds including estrogens

rs4587017	4	69947398	UGT2B7	Intron	T	G	0.334	0.327	conjugation of potentially toxic xenobiotics and endogenous compounds including estrogens
rs1042713	5	148206440	ADRB2	Exon	G	A	0.431	0.425	adrenergic signaling
rs12654778	5	148205741	ADRB2	5' near gene	A	G	0.365	0.392	adrenergic signaling
rs11959113	5	148848933	ADRB2	/	G	A, C	NA	NA	adrenergic signaling
rs1295686	5	131995843	IL13	Intron	T	C	0.327	0.313	anti-inflammatory cytokine
rs1799971	6	154360797	OPRM1	Intron	G	A	0.341	0.376	Opioid receptors
rs497976	6	154442512	OPRM1	3' near gene	T	G	0.102	0.116	Opioid receptors
rs533586	6	154413674	OPRM1	3' near gene	C	T	0.128	0.136	Opioid receptors
rs540825	6	154414446	OPRM1	Intron	A	T	0.071	0.079	Opioid receptors
rs548646	6	154418147	OPRM1	3' near gene	T	C	0.124	0.135	Opioid receptors
rs562859	6	154414573	OPRM1	Intron	C	T	0.130	0.136	Opioid receptors
rs563649	6	154407967	OPRM1	5' near gene	T	C	0.090	0.093	Opioid receptors
rs589046	6	154393138	OPRM1	5' near gene	T	C	0.149	0.147	Opioid receptors
rs639855	6	154436714	OPRM1	3' near gene	A	C	0.104	0.114	Opioid receptors
rs6912029	6	154360508	OPRM1	5'-UTR	T	G	0.089	0.093	Opioid receptors
rs9479757	6	154411344	OPRM1	Intron	A	G	0.059	0.058	Opioid receptors
rs1323042	6	154421844	OPRM1	3' near gene	G	T	0.222	0.223	Opioid receptors
rs1323040	6	154010889	OPRM1	5'-UTR	A	G	NA	NA	Opioid receptors
rs34059508	6	160154805	SLC22A1	Intron	G	A, C	NA	NA	Polyspecific organic cation transporters
rs12208357	6	160122116	SLC22A1	Intron	C	T	NA	NA	Polyspecific organic cation transporters
rs72552763	6	160139851	SLC22A1	Exon	GAT	-	NA	NA	Polyspecific organic cation transporters

rs34130495	6	160139792	SLC22A1	Intron	G	A	NA	NA	Polyspecific organic cation transporters
rs1799964	6	31542308	TNF	3' near gene	C	T	0.175	0.161	mediated peripheral and central inflammation
rs1800610	6	31543827	TNF	Intron	A	G	0.135	0.142	mediated peripheral and central inflammation
rs1800629	6	31543031	TNF	5' near gene	A	G	0.058	0.068	mediated peripheral and central inflammation
rs1045046	7	131186336	ABCB1	3'-UTR	C	G	0.479	0.497	ATP-dependent drug efflux pump
rs1045642	7	87138645	ABCB1	Exon	A	G	0.379	0.376	ATP-dependent drug efflux pump
rs1202170	7	87195106	ABCB1	Intron	C	T	0.354	0.346	ATP-dependent drug efflux pump
rs13229143	7	87219481	ABCB1	Intron	G	C	0.481	0.497	ATP-dependent drug efflux pump
rs2235033	7	87179143	ABCB1	Intron	G	A	0.355	0.346	ATP-dependent drug efflux pump
rs4437575	7	87139316	ABCB1	Intron	G	A	0.200	0.196	ATP-dependent drug efflux pump
rs1128503	7	87179601	ABCB1	Exon	G	A	0.351	0.346	ATP-dependent drug efflux pump
rs2235013	7	87178626	ABCB1	Intron	T	C	0.352	0.346	ATP-dependent drug efflux pump
rs2032582	7	87531302	ABCB1	Exon	A	C, T	NA	NA	ATP-dependent drug efflux pump
rs754891060	7	87544156	ABCB1	Exon	A	C, G	NA	NA	ATP-dependent drug efflux pump
rs2242480	7	99361466	CYP3A4	Intron	T	C	0.265	0.284	drug metabolizing enzymes
rs2069845	7	22770149	IL6	3'-UTR	G	A	0.012	0.016	cytokine involved in inflammatory response
rs1800795	7	22727026	IL6	5' near gene	C	G, T	NA	NA	cytokine involved in inflammatory response
rs7803773	7	79045055	MAGI2	5' near gene	C	A	0.243	0.248	transcription factor
rs1800783	7	150689397	NOS3	5' near gene	A	T	0.123	0.101	involved in nitric oxide synthesis

rs2073618	8	118951813	TNFRSF11B	Exon	G	C	NA	NA	TNF-receptor superfamily
rs1365098	8	54152683	OPRK1	Intron	A	C	0.384	0.381	Opioid receptors
rs6473799	8	54153123	OPRK1	Intron	G	A	0.384	0.383	Opioid receptors
rs7016778	8	54150105	OPRK1	Intron	T	A	0.080	0.098	Opioid receptors
rs7824175	8	54144174	OPRK1	Intron	G	C	0.087	0.092	Opioid receptors
rs7836120	8	54157539	OPRK1	Intron	C	T	0.243	0.257	Opioid receptors
rs963549	8	54141824	OPRK1	3'-UTR	T	C	0.073	0.073	Opioid receptors
rs10504151	8	53245680	OPRK1	Intron	A	G	NA	NA	Opioid receptors
rs16918875	8	53229594	OPRK1	Exon	G	A	NA	NA	Opioid receptors
rs3780039	8	139664421	KCNK9	5' near gene	A	C	NA	NA	pH-dependent potassium channel
rs11166921	8	139695512	KCNK9	5' near gene	A	C, G, T	NA	NA	pH-dependent potassium channel
rs17180299	9	82944202	SPON1	/	G	A	0.097	0.093	promotes the attachment of spinal cord and sensory neuron cells and the outgrowth of neurites
rs2756109	10	101558746	ABCC2	Intron	T	G	0.308	0.307	ATP-dependent drug efflux pump
rs1800545	10	112837538	ADRA2A	5'-UTR	A	G	0.171	0.152	adrenergic signaling
rs11195419	10	112839368	ADRA2A	3'-UTR	A	C	0.174	0.154	adrenergic signaling
rs553668	10	111079821	ADRA2A	3'-UTR	A	G, T	NA	NA	adrenergic signaling
rs580253	11	105029761	CASP1	Exon	G	A	NA	NA	a member of the cysteine-aspartic acid protease (caspase) family
rs554344	11	105024470	CASP5	5'-UTR	G	A, C	NA	NA	a member of the cysteine-aspartic acid protease (caspase) family
rs6265	11	27679916	BDNF	Exon	T	C	0.465	0.474	neuron growth and survival factor; major regulator of synaptic transmission and plasticity in adults

rs618027	11	124584312	/	/	C	G	0.376	0.413	Opioid receptors
rs7965399	12	102891686	LOC105369944	Intron	C	T	0.286	0.276	transcription factor
rs1718125	12	121593019	P2RX7	3' near gene	T	C	0.351	0.322	extracellular ATP-gated ion channel
rs7958311	12	121605355	P2RX7	Exon	A	G	0.448	0.460	extracellular ATP-gated ion channel
rs10770367	12	18663922	PIK3C2G	Intron	C	A	0.375	0.316	play roles in signaling pathways
rs167769	12	57503775	STAT6	5'-UTR	T	C	0.221	0.203	plays a central role in exerting IL4 mediated biological responses
rs3024971	12	57493727	STAT6	Intron	G	T	0.059	0.065	plays a central role in exerting IL5 mediated biological responses
rs841718	12	57492996	STAT6	Intron	A	G	0.304	0.276	plays a central role in exerting IL6 mediated biological responses
rs9524885	13	95935589	ABCC4	5' near gene	T	C	0.336	0.348	ATP-dependent drug efflux pump
rs3783641	14	55360139	GCH1	Intron	A	T	0.122	0.112	rate-limiting enzyme for BH4 synthesis
rs4411417	14	55320563	GCH1	Intron	C	T	0.362	0.347	rate-limiting enzyme for BH5 synthesis
rs752668	14	98366896	GCH1	/	G	A	0.276	0.290	rate-limiting enzyme for BH6 synthesis
rs8904	14	35871217	NFKB1A	3'-UTR	A	G	0.398	0.412	inhibits the activity of NF-Kappa-B complexes
rs6572493	14	22503969	LOC112267867	Intron	A	G	NA	NA	an RNA Gene
rs1805009	16	89920138	MC1R	5' near gene	G	A, C	NA	NA	melanocyte-stimulating hormone receptor

rs4793665	17	48712087	ABCC3	5' near gene	C	T	0.111	0.107	ATP-dependent drug efflux pump
rs1045280	17	4622638	ARRB2	Exon	C	T	0.190	0.181	adrenergic signaling
rs16954146	17	4618472	ARRB2	Intron	A	G	0.189	0.182	adrenergic signaling
rs2036657	17	4625159	ARRB2	3' near gene	G	A	0.189	0.184	adrenergic signaling
rs2271167	17	4622880	ARRB2	Intron	A	G	0.180	0.170	adrenergic signaling
rs3786047	17	4615098	ARRB2	Exon	A	G	0.189	0.180	adrenergic signaling
rs4790693	17	4711302	ARRB2	5' near gene	C	A, G, T	NA	NA	adrenergic signaling
rs7208257	17	4717202	ARRB2	Exon	C	A, G, T	NA	NA	adrenergic signaling
rs12948783	17	74499400	RHBDF2	5' near gene	A	G	0.103	0.111	play roles the devel-opment of inflammation
rs222747	17	3493200	TRPV1	Exon	G	C	0.386	0.383	nonselective cation channel that senses environmental irritants
rs4499491	20	43721419	KCNS1	3'-UTR	C	A	0.270	0.245	voltage-gated potassium channel subunit
rs734784	20	43723627	KCNS1	Exon	C	T	0.203	0.194	voltage-gated potassium channel subunit
rs2834167	21	34640788	IL10RB	Exon	A	G	0.417	0.445	inhibits the synthesis of a number of cytokines
rs2070995	21	39086965	KCNJ6	5' near gene	T	C	0.387	0.370	potassium channel that regulates insulin secretion by glucose and neurotransmitters
rs2835914	21	39098850	KCNJ6	Intron	C	G	0.499	0.486	potassium channel that regulates insulin secretion by glucose and neurotransmitters

rs2836050	21	39284835	KCNJ6	Intron	T	C	0.346	0.390	potassium channel that regulates insulin secretion by glucose and neurotransmitters
rs8129919	21	39254540	KCNJ6	Intron	G	A	0.494	0.495	potassium channel that regulates insulin secretion by glucose and neurotransmitters
rs2284015	22	37096573	CACNG2	5' near gene	G	C	0.332	0.297	voltage-dependent calcium channel subunit
rs4820242	22	36982675	CACNG2	5' near gene	G	A	0.461	0.460	voltage-dependent calcium channel subunit
rs2284017	22	37096927	CACNG2	5' near gene	T	C	0.481	0.483	voltage-dependent calcium channel subunit
rs2020917	22	19928884	COMT	5' near gene	T	C	0.297	0.304	neurotransmitter degradation
rs4633	22	19950235	COMT	Exon	T	C	0.233	0.276	neurotransmitter degradation
rs4646312	22	19948337	COMT	5' near gene	C	T	0.362	0.337	neurotransmitter degradation
rs5993882	22	19937533	COMT	5' near gene	G	T	0.106	0.085	neurotransmitter degradation
rs6267	22	19950263	COMT	5' near gene	T	G	0.061	0.049	neurotransmitter degradation
rs6269	22	19949952	COMT	5' near gene	G	A	0.359	0.332	neurotransmitter degradation
rs4818	22	19951207	COMT	5' near gene	G	C	0.364	0.327	neurotransmitter degradation
rs8136867	22	21850504	MAPK1	Intron	G	A	NA	NA	MAP kinase family
rs1080985	22	42528382	CYP2D6	5' near gene	C	G	0.142	0.130	drug metabolizing enzymes

MAF: minor allele frequency. There were 26 SNPs without their MAF data because they did not enter the final analysis.

Supplementary Table 2 Non-genetic factors associated with opioid response in univariate analyses.

Variables	**Opioid dose**	**Pain relief**	**Opioid dose(class)**	**Pain relief(class)**	**Constipation**
Age	0.390	0.953	0.463	0.936	**0.021**
Gender	0.152	0.127	0.523	0.176	0.552
BMI	0.204	0.914	0.520	0.913	0.264
Tumor diagnosis	0.172	0.463	0.411	0.446	**0.005**
PS	**0.006**	**0.001**	**0.028**	0.129	0.079
Tumor metastasis status					
Bone	**0.046**	0.807	0.059	0.053	0.057
Liver	0.566	0.074	0.322	0.760	0.930
CNS	0.877	0.480	0.324	0.518	0.926
Lung	0.542	**0.014**	0.612	0.884	0.506
Other	0.256	0.335	0.091	0.275	0.658
Opioid tolerance	**0.000**	0.251	**0.000**	**0.024**	**0.010**
Pain category	0.919	0.595	0.922	0.645	0.259
NRS2002 score	0.210	0.875	0.366	**0.030**	0.934
Number of adjuvant analgesics	**0.000**	0.741	**0.001**	0.119	0.149
SDS score	**0.009**	**0.001**	**0.049**	**0.000**	**0.017**
ALT (U/L)	0.491	0.764	0.553	0.854	0.872
AST (U/L)	0.458	0.863	0.406	0.554	0.621
LDH (U/L)	0.405	1.000	1.000	0.881	0.153
Creatinine serum concentration (μmol/L)	0.064	0.584	0.493	0.392	0.473
Opioid	0.054	0.311	**0.008**	0.500	0.283
Time since onset of pain symptoms (mo)	0.059	0.259	**0.001**	0.865	0.497
Time since start of opioid treatment (mo)	0.699	0.574	1.000	0.212	0.255
Pain relief (%)	**0.000**	/	**0.008**	/	/
Opioid dose（OEDD）	/	**0.001**	/	**0.000**	**0.000**
Age (class)	0.113	0.446	0.412	0.067	0.755
BMI (class)	0.306	**0.003**	0.680	0.419	0.339
Time since start of opioid treatment(class)	**0.000**	0.900	**0.000**	**0.002**	**0.006**

Data in boldface are p＜0.05; BMI, body mass index; PS, performance status; NRS2002: nutritional risk screening scoring; CNS, central nervous system; SDS, Self-Rating Depression Scale; ALT, alanine aminotransferase; AST, aspartate transaminase; LDH, lactate dehydrogenase; mo, month; OEDD, oral oxycodone equivalent daily dose.

Supplementary Table 3 SNPs with an uncorrected p value of less than 0.05 in the discovery sample in the dominant model of the three phenotypes

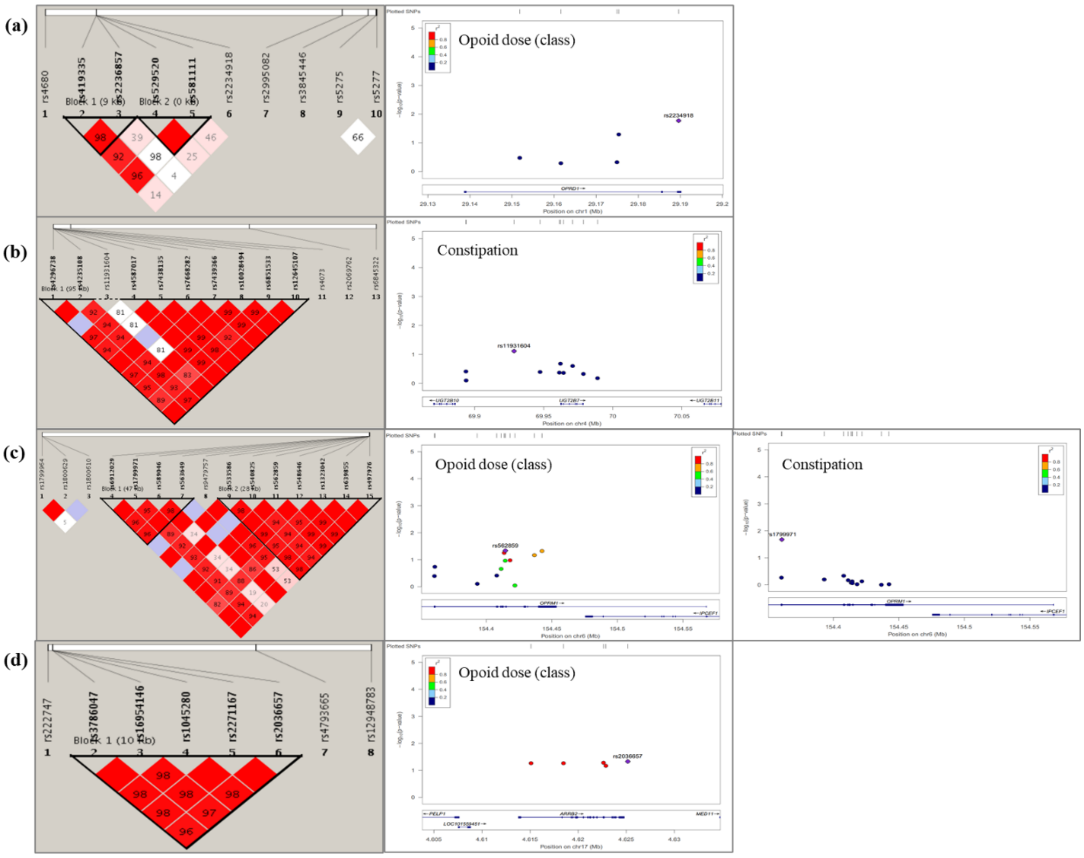
phenotype	**Gene**	**SNP**	**minor allele**	**major allele**	**Development sample (n = 572)**			**Validation sample (n = 286)**	
					β	P^1	P^2	β	P^1
Opioid dose (logOEDD)	ABCC4	rs9524885	T	C	-0.050	0.005	0.525	0.006	0.825
	OPRM1	rs1799971	G	A	0.043	0.014	0.670	-0.003	0.918
	TNF	rs1799964	C	T	0.043	0.023	0.670	-0.045	0.105
	STAT6	rs167769	T	C	-0.040	0.025	0.670	-0.048	0.065
	OPRD1	rs2234918	C	T	-0.040	0.030	0.670	-0.015	0.554
	OPRM1	rs6912029	T	G	0.046	0.046	0.839	-0.019	0.570
Pain relief	ABCC4	rs9524885	T	C	0.362	0.002	0.167	-0.025	0.891
	OPRM1	rs6912029	T	G	-0.408	0.006	0.502	0.174	0.393
	OPRM1	rs563649	T	C	-0.397	0.008	0.590	0.109	0.595
	NFKB1A	rs8904	A	G	-0.287	0.016	0.430	0.050	0.760
	OPRM1	rs1799971	G	A	-0.245	0.034	0.696	-0.137	0.395
	STAT6	rs167769	T	C	0.241	0.039	0.696	0.280	0.081
	CREB1	rs12645107	A	G	0.235	0.044	0.696	-0.215	0.186
					OR	P^1	P^2	OR	P^1
Opioid dose (class)	ABCC4	rs9524885	T	C	1.915	0.004	0.408	0.789	0.493
	OPRD1	rs2234918	A	T	1.777	0.017	0.471	1.396	0.353
	RHBDF2	rs12948783	A	G	1.998	0.026	0.471	1.200	0.668
	OPRK1	rs7836120	C	T	1.662	0.028	0.471	0.770	0.699
	OPRK1	rs963549	T	C	0.547	0.042	0.471	2.422	0.109
	OPRM1	rs562859	C	T	1.747	0.047	0.471	0.983	0.963

Pain relief (class)	ARRB2	rs2036657	G	A	0.633	0.047	0.471	0.937	0.537
	OPRM1	rs497976	T	G	1.845	0.048	0.471	0.760	0.486
	STAT6	rs3024971	G	T	0.139	0.017	0.672	0.112	0.103
	UGT2B7	rs7438135	G	A	0.206	0.030	0.672	1.507	0.749
	UGT2B7	rs4587017	T	G	0.206	0.030	0.672	1.507	0.749
	UGT2B7	rs7439366	T	C	0.207	0.030	0.672	1.507	0.749
	UGT2B7	rs6851533	T	C	0.209	0.032	0.672	1.507	0.749
	IL13	rs1295686	T	C	3.548	0.041	0.723	0.250	0.323
Constipation	PTGS2	rs5275	G	A	0.528	0.001	0.093	0.570	0.030
	OPRM1	rs1799971	G	A	1.513	0.020	0.787	0.886	0.778
	CYP2D6	rs1080985	C	G	1.520	0.042	0.787	0.580	0.056
	LOC105369944	rs7965399	C	T	0.693	0.044	0.787	0.818	0.641

OR: odds ratio; P^1: the uncorrected p value, P^2: *p* value corrected by FDR_BH.

Supplementary Table 4 All the haplotypes constructed in this study and their frequency

Gene	SNPs	Chr	Haplotype	Haplotype frequency Development sample (n = 572)	Haplotype frequency Validation sample (n = 286)
OPRD1	rs419335, rs2236857	1	AT	0.809	0.822
			GC	0.104	0.091
			GT	0.088	0.083
OPRD1	rs529520, rs581111	1	CG	0.862	0.881
			AA	0.077	0.082
			AG	0.061	0.037
P2RY12	rs3732765, rs9859538	3	GG	0.857	0.837
			AA	0.14	0.154
UGT2B7	rs4296738, rs4235108, rs4587017, rs7438135, rs7668282, rs7439366, rs10028494, rs6851533, rs12645107	4	GGGATCACA	0.363	0.396
			GATGTTCTG	0.247	0.233
			AGGATCACG	0.17	0.165
			GAGACCACG	0.078	0.084
			GATGTTATG	0.076	0.072
			GAGATCACG	0.044	0.023
ADRB2	rs12654778, rs1042713	5	GG	0.429	0.422
			AA	0.362	0.389
			GA	0.207	0.186
OPRM1	rs6912029, rs1799971, rs589046, rs563649	6	GACC	0.51	0.475
			GGCC	0.34	0.377
			TATT	0.086	0.089
			GATC	0.058	0.051
ABCB1	rs1045642, rs4437575	7	GA	0.423	0.428
			AA	0.377	0.377
			GG	0.199	0.195
ABCB1	rs2235013, rs2235033, rs1128503, rs1202170	7	CAAT	0.638	0.649
			TGGC	0.346	0.339
ADRA2A	rs1800545, rs11195419	10	GC	0.826	0.846
			AA	0.17	0.153
STAT6	rs841718, rs3024971	12	GT	0.696	0.727
			AT	0.245	0.208
			AG	0.059	0.065
ARRB2	rs3786047, rs16954146, rs1045280, rs2271167, rs2036657	17	GGTGA	0.807	0.809
			AACAG	0.178	0.167
CACNG2	rs2284015, rs2284017	22	CC	0.52	0.517
			GT	0.332	0.298
			CT	0.148	0.185



Supplementary Fig. 1 Linkage disequilibrium (LD) and locuszoom plot of association results of singlenucleotide polymorphisms (SNPs) in different phenotypes. (a) Chr. 1 OPRD1 gene, (b) Chr. 4 UGT2B7 gene, (c) Chr. 6 OPRM1, (d) Chr. 17 ARRB2 gene. For each gene, Haploview LD graph of SNPs was visualized using the Haploview software 4.2. LD was calculated using D’ (0= no disequilibrium; 1= maximum disequilibrium). The numbers inside the squares are 100 D’. In the locuszoom plot, the left vertical axis shows association P-values in the develop stage on the −log10 scale and the horizontal axis shows the chromosomal position. The purple diamond is the most significant SNP at each plot. LD (r^2) was estimated from the 1000 Genomes Project ASN data (Nov2014, build GRCh37/hg19), and was colour coded as a heatmap from dark blue ($0 \geq r^2 > 0.2$) to red ($0.8 \geq r^2 > 1.0$).