

**Polymorphisms of *SLCO1B1* rs4149056 and *SLC22A1* rs2282143 are associated with responsiveness to acitretin in psoriasis patients**

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**Conflicts of interest**

All the authors confirmed that there were no conflicts of interest.

Patient 1



Patient 2



Patient 3

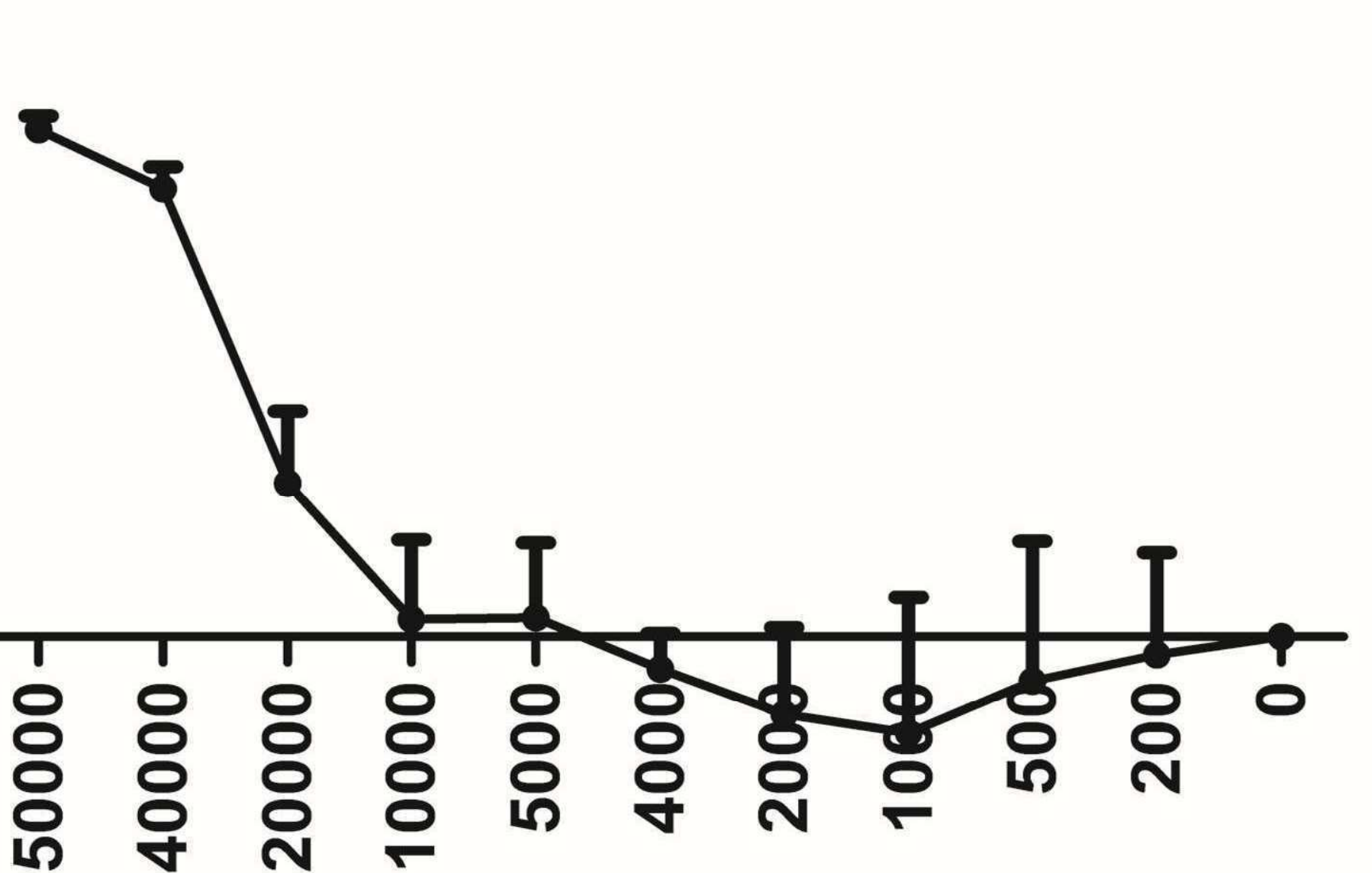


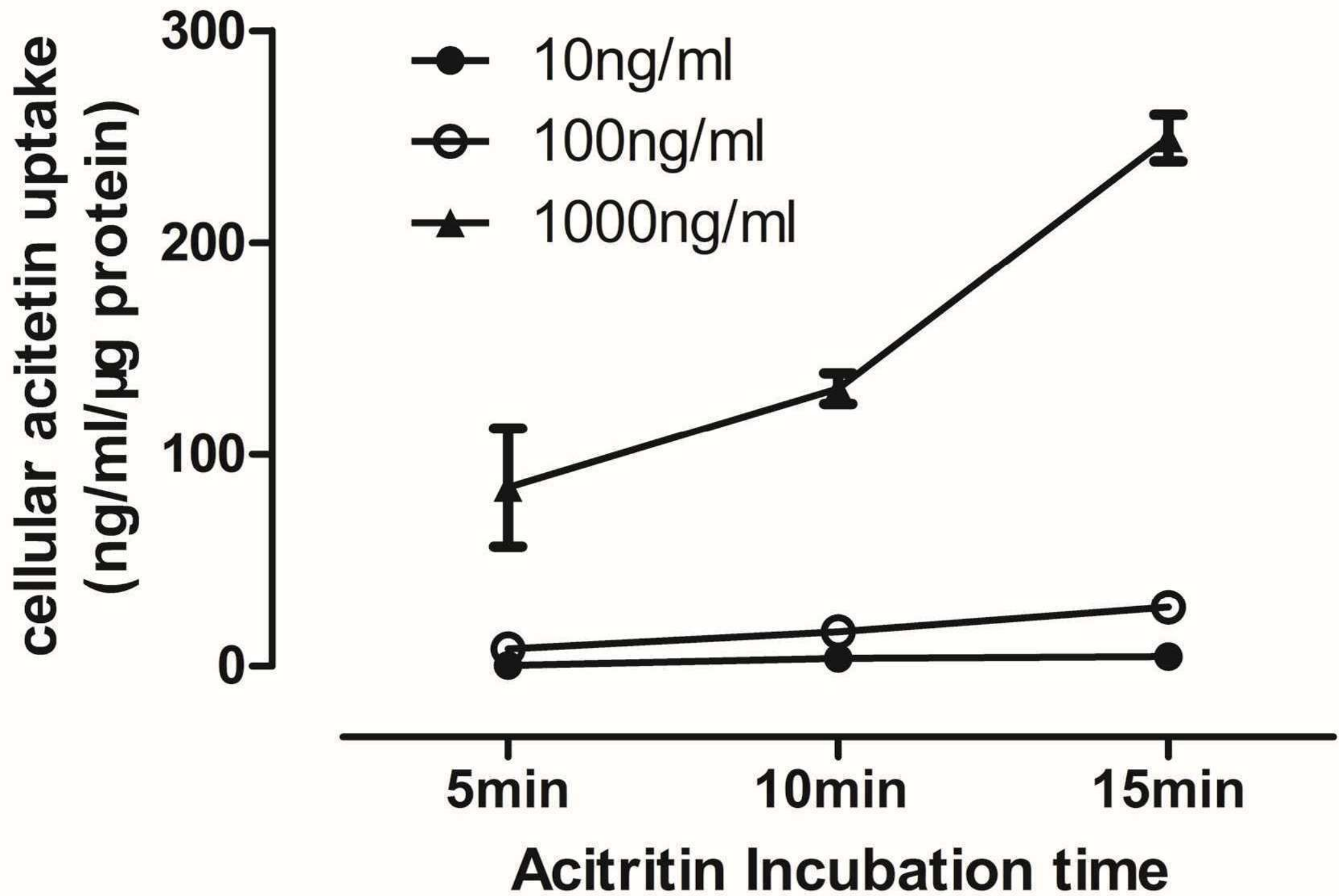
**cell proliferation inhibition rate**

1.0  
0.5  
0.0  
-0.5

50000  
40000  
20000  
10000  
5000  
4000  
2000  
1000  
500  
200  
0

**Acitretin incubation concentration(ng/ml)**





## **Legends of Supplementary Figures**

**Supplementary Figure S1.** Efficacy of acitretin varied in psoriasis patients

Legends: All patients were treated with acitretin 30 mg/day plus calcipotriol ointment. With treatment for 8 weeks, patient 1 was classed as a responder with PASI improvement >50%, and patient 2 was classed as a non-responder with PASI improvement <50%. Patient 3 was classed as a non-responder, with markedly increased disease severity after 1-week treatment with acitretin.

**Supplementary Figure S2.** The effect of different acitretin concentration incubation on HEK293 cells proliferation.

Legends: With acitretin concentration no more than 200 ng/ml, there was no significant influence on cell proliferation. While, when the concentration was up to 500 ng/ml, there were notable changes in cell proliferation.

**Supplementary Figure S3.** Incubation time 15min for acitretin uptake

Legends: As the incubation time increased, cellular acitretin uptake was saturated at 10 min with a concentration of 10 or 100 ng/ml. When acitretin concentration reached 1000 ng/ml, the uptake capability was still increasing at 15 min.

Supplement Table 1. The SNPs list of vera code adme core panel					
Assay	Gene Symbol	PrimaryName	Nucleotide Change	Effect	RefSeq ID
1	ABCB1	1236C>T	c.1236C>T	-	rs1128503
2	ABCB1	-129 T>C)	c.-129C>T	-	rs3213619
3	ABCB1	2677nt G>T>A	c.2677G>T>A	-	rs2032582
4	ABCB1	C3435ntT	c.3435C>T	-	rs1045642
5	ABCC2	-24C>T	c.-24C>T	-	rs717620
6	ABCC2	A1450T	c.4348G>A	p.A1450T	rs56296335
7	ABCC2	I1324I	c.3972C>T	p.I1324I	rs3740066
8	ABCC2	R768W	c.2302C>T	p.R768W	rs56199535
9	ABCC2	S789F	c.2366C>T	p.S789F	rs56220353
10	ABCC2	V417I	c.1249G>A	p.V417I	rs2273697
11	ABCG2	421nt C>A	c.421C>A	p.Q141K	rs2231142
12	ABCG2	Q126X	c.376C>T	p.Q126X	rs72552713
13	CYP1A1	*2 (I462V)	2455A>G	p.I462V	rs1048943
14	CYP1A1	*3	3205T>C	-	rs1800031
15	CYP1A1	*4	2453C>A	p.T461N	rs1799814
16	CYP1A1	*5	2461C>A	p.R464S	rs41279188
17	CYP1A1	*6	1636G>T	p.M331I	rs56313657
18	CYP1A1	*7	2346-2347insT	Frameshift	rs72547510
19	CYP1A1	*8	2414T>A	p.I448N	rs72547509
20	CYP1A2	*1C	-3860G>A	-	rs2069514
21	CYP1A2	*1F	-163C>A	-	rs762551
22	CYP1A2	*1K	-729C>T	-	rs12720461
23	CYP1A2	*7	3533G>A	Splicing defect	rs56107638
24	CYP2A6	*11	c.670T>C	p.S224P	rs28399447
25	CYP2A6	*17	c.1093G>A	p.V365M	rs28399454
26	CYP2A6	*1B	-	-	-
27	CYP2A6	*2	c.479T>A	p.L160H	rs1801272
28	CYP2A6	*20	c.587-588delAA	Frameshift	rs28399444
29	CYP2A6	*4			NA
30	CYP2A6	*6	c.383G>A	p.R128Q	rs4986891
31	CYP2A6	*7	c.1412T>C	p.I471T	rs5031016
32	CYP2A6	*8	c.1454G>T	p.R485L	rs28399468
33	CYP2A6	*9	g.-48T>G	TATA box	rs28399433
34	CYP2B6	*16	c.983T>C	p.I328T	rs28399499
35	CYP2B6	*2	c.64C>T	p.R22C	rs8192709
36	CYP2B6	*28	c.1132C>T	p.R378X	rs34097093
37	CYP2B6	*8	c.415A>G	p.K139E	rs12721655
38	CYP2B6	*9 (*6)	c.516G>T	p.Q172H	rs3745274
39	CYP2C19	*12	c.1473A>C	p.X491C; 26 extra AA	rs55640102
40	CYP2C19	*17	g.-806C>T	-	rs12248560

41	CYP2C19	*2	c.681G>A	Splicing defect	rs4244285
42	CYP2C19	*3	c.636G>A	p.W212X	rs4986893
43	CYP2C19	*4	c.1A>G	GTG start codon	rs28399504
44	CYP2C19	*5	c.1297C>T	p.R433W	rs56337013
45	CYP2C19	*6	c.395G>A	p.R132Q	rs72552267
46	CYP2C19	*7	g.19294T>A	Splicing defect	rs72558186
47	CYP2C19	*8	c.358T>C	p.W120R	rs41291556
48	CYP2C8	*2	c.805A>T	p.I269F	rs11572103
49	CYP2C8	*3	c.1196A>G	p.K399R	rs10509681
50	CYP2C8	*4	c.792C>G	p.I264M	rs1058930
51	CYP2C8	*5	c.475delA	Frameshift	rs72558197
52	CYP2C8	*7	c.556C>T	p.R186X	rs72558195
53	CYP2C8	*8	c.556C>G	p.R186G	rs72558195
54	CYP2C9	*10	c.815A>G	p.E272G	rs9332130
55	CYP2C9	*11	c.1003C>T	p.R335W	rs28371685
56	CYP2C9	*12	c.1465C>T	p.P489S	rs9332239
57	CYP2C9	*13	c.269T>C	p.L90P	rs74052158
58	CYP2C9	*15	c.485C>A	p.S162X	rs72558190
59	CYP2C9	*2	c.430C>T	p.R144C	rs1799853
60	CYP2C9	*25	c.353-362delAGAAATGGAA	Frameshift	rs72558188
61	CYP2C9	*3	c.1075A>C	p.I359L	rs1057910
62	CYP2C9	*4	c.1076T>C	p.I359T	rs56165452
63	CYP2C9	*5	c.1080C>G	p.D360E	rs28371686
64	CYP2C9	*6	818delA (cDNA)	Frameshift	rs9332131
65	CYP2C9	*8	c.449G>A	p.R150H	rs7900194
66	CYP2C9	*9	c.752A>G	p.H251R	rs2256871
67	CYP2D6	*10	100C>T	p.P34S	rs1065852
68	CYP2D6	*11	883G>C	Splicing defect	rs5030863
69	CYP2D6	*12	124G>A	p.G42R	rs5030862
70	CYP2D6	*14	1758G>A	p.G169R	rs5030865
71	CYP2D6	*15	137-138insT	Frameshift	rs72549357
72	CYP2D6	*17	1023C>T	p.T107I	rs28371706
73	CYP2D6	*18	4125-4133insGTGCCCACT	p.468-470dupVPT	NA
74	CYP2D6	*19	2539-2542delAACT	Frameshift	rs72549353
75	CYP2D6	*20	1973-1974insG	Frameshift	rs72549354
76	CYP2D6	*21	2573-2574insC	Frameshift	rs72549352
77	CYP2D6	*2a	-1584C>G		rs1080985
78	CYP2D6	*3	2549delA	Frameshift	rs35742686
79	CYP2D6	*38	2587-2590delGACT	Frameshift	rs72549351
80	CYP2D6	*4	1846G>A	Splicing defect	rs3892097

81	CYP2D6	*41	2988G>A	Splicing defect	rs28371725
82	CYP2D6	*42	3259-3260insGT	Frameshift	rs72549346
83	CYP2D6	*44	2950G>C	Splicing defect	rs72549349
84	CYP2D6	*5			NA
85	CYP2D6	*56	3201C>T	p.R344X	rs72549347
86	CYP2D6	*6	1707delT	Frameshift	rs5030655
87	CYP2D6	*7	2935A>C	p.H324P	rs5030867
88	CYP2D6	*8	1758G>T	p.G169X	rs5030865
89	CYP2D6	*9	2615-2617delAAG	p.K281del	rs5030656
90	CYP2E1	*2	1132G>A	p.R76H	rs72559710
91	CYP3A4	*1G	IVS10+12G>A	-	rs2242480
92	CYP3A4	*2	c.664T>C	p.S222P	rs55785340
93	CYP3A4	*20	c.1461-1462insA	Frameshift	rs67666821
94	CYP3A4	*6	c.830-831insA	Frameshift	rs4646438
95	CYP3A5	*10(F446S)	29753T>C	c.F446S	rs41279854
96	CYP3A5	*3	6986A>G	Splicing defect	rs776746
97	CYP3A5	*5	12952T>C	Splicing defect	rs55965422
98	CYP3A5	*6	14690G>A	Splicing defect	rs10264272
99	CYP3A5	*7	27131-27132insT	Frameshift	rs41303343
100	DPYD	*10	c.2983G>T	p.V995F	rs1801268
101	DPYD	*2A	IVS14+1G>A	-	rs3918290
102	DPYD	*7	c.295-298delTCAT	-	rs72549309
103	DPYD	*8	-	p.R235W	rs1801266
104	DPYD	*9A	c.85T>C	p.C29R	rs1801265
105	DPYD	*9B	c.2657G>A	p.R886H	rs1801267
106	GSTM1	*B	c.519G>C	p.K172N	rs1065411
107	GSTM1	CNV	-	-	-
108	GSTP1	*A_*B_*C_*D	c.313A>G	p.I105V	rs1695
109	GSTP1	*A_*B_*C_*D	c.341C>T	p.A114V	rs1138272
110	GSTT1	CNV	-	-	-
111	NAT1	*11	c.-344C>T	-	rs4986988
112	NAT1	*11	c.-40A>T	-	rs4986989
113	NAT1	*11	c.445G>A	p.V149I	rs4987076
114	NAT1	*11	c.459G>A	p.T153T	rs4986990
115	NAT1	*11	c.640T>G	p.S214A	rs4986783
116	NAT1	*14	c.560G>A	p.R187Q	rs4986782
117	NAT1	*15	c.559C>T	p.R187X	rs5030839
118	NAT1	*17	c.190C>T	p.R64W	rs56379106
119	NAT1	*19	c.97C>T	p.R33X	rs56318881
120	NAT1	*22	c.752A>T	p.D251V	rs56172717
121	NAT1	*5(350-351G>C)	c.350-351GG>CC	p.R117T	rs72554606



122	NAT1	*5(497-499G>C)	c.497-499GGG>CCC	p.R166T; E167Q	rs72554608
123	NAT1	*5(884A>G)	c.884A>G	-	rs55793712
124	NAT1	*5(976delA)	c.976delA	-	rs72554612
125	NAT2	*11	c.481C>T	p.L161L	rs1799929
126	NAT2	*12	c.803A>G	p.K268R	rs1208
127	NAT2	*13	c.282C>T	p.Y94Y	rs1041983
128	NAT2	*14	c.191G>A	p.R64Q	rs1801279
129	NAT2	*19	c.190C>T	p.R64W	rs1805158
130	NAT2	*5	c.341T>C	p.I114T	rs1801280
131	NAT2	*6	c.590G>A	p.R197Q	rs1799930
132	NAT2	*7	c.857G>A	p.G286E	rs1799931
133	SLC15A2	A284A	c.852G>A	p.A284A	rs2293616
134	SLC15A2	L350F	c.1048C>T	p.L350F	rs2257212
135	SLC15A2	P409S	c.1225C>T	p.P409S	rs1143671
136	SLC15A2	R509K	c.1526G>A	p.R509K	rs1143672
137	SLC22A1	420del	c.1258-1260delATG	p.M420del	rs35167514; rs34305973; rs35191146
138	SLC22A1	C88R	c.262T>C	p.C88R	rs55918055
139	SLC22A1	G220V	c.659G>T	p.G220V	rs36103319
140	SLC22A1	G401S	c.1201G>A	p.G401S	rs34130495
141	SLC22A1	G465R	c.1393G>A	p.G465R	rs34059508
142	SLC22A1	M408V	c.1222A>G	p.M408V	rs628031
143	SLC22A1	P283L	c.848C>T	p.P283L	rs4646277
144	SLC22A1	P341L	c.1022C>T	p.P341L	rs2282143
145	SLC22A1	R287G	c.859C>G	p.R287G	rs4646278
146	SLC22A1	R61C	c.181C>T	p.R61C	rs12208357
147	SLC22A2	K432Q	c.1294A>C	p.K432Q	rs8177517
148	SLC22A2	M165I	c.495G>A	p.M165I	rs8177507
149	SLC22A2	P54S	c.160C>T	p.P54S	rs8177504
150	SLC22A2	R400C (*7.1)	c.1198C>T	p.R400C	rs8177516
151	SLC22A2	S270A (*4.1)	c.808G>T	p.S270A	rs316019
152	SLC22A6	R50H	c.149G>A	p.R50H	rs11568626
153	SLCO1B1	*10	c.1964A>G	p.D655G	rs56199088
154	SLCO1B1	*11	c.2000A>G	p.E667G	rs55737008
155	SLCO1B1	*12			
156	SLCO1B1	*13			
157	SLCO1B1	*1B	c.388G>A	p.N130D	rs2306283
158	SLCO1B1	*2	c.217T>C	p.F73L	rs56101265
159	SLCO1B1	*3(E156G)	c.467A>G	p.E156G	rs72559745
160	SLCO1B1	*3(V82A)	c.245T>C	p.V82A	rs56061388
161	SLCO1B1	*5	c.521T>C	p.V174A	rs4149056

162	SLCO1B1	*6	c.1058T>C	p.I353T	rs55901008
163	SLCO1B1	*9	c.1463G>C	p.G488A	rs59502379
164	SLCO2B1	*3	c.1457C>T	p.S486F	rs2306168
165	SLCO1B3	M233I	c.699G>A	p.M233I	rs7311358
166	SLCO1B3	S112A	c.334T>G	p.S112A	rs4149117
167	SULT1A1	*2	c.638G>A	p.R213H	rs9282861
168	SULT1A1	*3(M223V)	c.667G>A	p.V223M	rs1801030
169	SULT1A1	*4(R37Q)		p.R37Q	rs72547527
170	SULT1A1	Null(deletion)			NA
171	TPMT	*2	c.238G>C	p.A80P	rs1800462
172	TPMT	*3a			
173	TPMT	*3b	c.460G>A	p.A154T	rs1800460
174	TPMT	*3c	c.719A>G	p.Y240C	rs1142345
175	TPMT	*8	c.644G>A	p.R215H	rs56161402
176	UGT1A1	*27	c.686C>A	p.P229Q	rs35350960
177	UGT1A1	*29	c.1099C>G	p.R367G	rs55750087
178	UGT1A1	*6	c.211G>A	p.G71R	rs4148323
179	UGT1A1	*60	-3279T>G	-	rs4124874
180	UGT1A1	*7	c.1456T>G	p.Y486D	rs34993780
181	UGT2B15	*2	c.253G>T	p.D85Y	rs1902023
182	UGT2B17	CNV			NA
183	UGT2B7	*2	c.802T>C	p.H268Y	rs7439366
184	VKORC1	-1639G>A	-1639G>A	-	rs9923231

Supplement Table 2. The demographic data and PASI of the patients in two phases

Phase/ Genotype	Effective Group	Age		BMI		PASI baseline	
		Value	P value	Value	P value	Value	P value
Discovery phase	PASI<50(23)	45.35±14.06	0.066	23.11±3.90	0.936	10.41±7.08	0.477
	PASI>50(23)	36.95±16.03		23.18±2.29		12.08±8.57	
Verification phase	PASI<50(57)	42.45±14.00	**0.013	22.73±5.19	0.609	10.73±7.41	0.671
	PASI>50(48)	35.30±15.67		22.32±2.49		11.28±6.21	
	SLCO1B1 rs4149056 TT	38.68±12.14	0.369	22.91±2.41	0.466	11.17±4.84	0.381
	SLCO1B1 rs4149056TC+CC	39.76±14.82		22.77±3.49		11.20±4.10	
	SLC22A1 rs2282143 CC	40.41±13.64	0.576	22.72±3.63	0.468	12.24±5.24	0.128
	SLC22A1 rs2282143CT+TT	40.39±11.25		22.90±2.52		10.23±4.12	

Supplement Table 3. The polymorphisms of rs4149056T>C and rs2282143C>T frequencies in patients with PASI>10

phases	SLC22A1 Rs2282143					SLCO1B1 Rs4149056						
	Genotypes/ alleles	PASI<5 0	PASI>5 0	P value	OR[95CI]	HWE	Genotype s/alleles	PASI< 50	PASI> 50	P value	OR[95CI]	HW
Discover y Phase	CC	12	3	P<0.001	40.000[3.57 9, 447.034]	0.171	TT	12	6	P=0.01	14.000[1.385, 141.485]	0.354
	CT+TT	1	10				TC	1	7			
	C	25	16	P=0.002	15.625[1.82 1,134.040]		T	25	19	P=0.02	9.211[1.043,81 .361]	
Verificati on Phase	CC	28	19	P=0.012	5.404[1.328, 21.983]	0.311	TT	29	24	P=0.11	3.625[0.669, 19.630]	0.584
	CT+TT	3	11				TC	2	6			
	C	59	49	P=0.019	4.415[1.166, 16.720]		T	60	54	P=0.13	3.333[0.645,17 .218]	
Total samples	CC	40	22	P<0.001	9.545[2.907, 31.348]	0.118	TT	41	30	P=0.00	5.922[1.549, 22.635]	0.345
	CT+TT	4	21				TC+TT	3	13			
	C	84	65	P<0.001	6.785[2.220, 20.736]		T	85	73	P=0.00	5.046[1.384, 18.399]	
	T	4	21				C	3	13			

Supplement Table 4. The haplotypes of rs2282143-rs4149056 polymorphisms distribution in response and non-response groups.

Haplotypes (rs2282143-rs4149056)	Response (N, %)	Non-response (N, %)	Sig.
CC-TT	32(45.07%)	63(78.75%)	P<0.001
CT-TT/CC-CT	21(29.58%)	14(17.5%)	
CT-CT	18(25.35%)	3(3.75%)	
CC-TT/CT-TT/CC-CT (<2 variants)	53(74.65%)	77(96.25%)	P<0.001
CT-CT	18(25.35%)	3(3.75%)	