

表 2-2-A (続き)

Sample	HLA-A 遺伝子		HLA-B 遺伝子		HLA-Cw 遺伝子	
	遺伝子型	セロタイプ	遺伝子型	セロタイプ	遺伝子型	セロタイプ
HT42	*0206/*2601	A2/A26	*3501/*4002	B35/B61	*0303/*0304	Cw9/Cw10
HT43	*2601/*2601	A26/A26	*1501/*5101	B62/B51	*0102/*0304	Cw1/Cw10
HT44	*2402/*2603	A24/A26	*1518/*3501	B71/B35	*0303/*0704	Cw9/Cw7
HT45	*1101/*3303	A11/A33	*4001/*440301	B60/B44	*0304/*1403	Cw10/Cw1/blank
HT47	*2402/*2601	A24/A26	*4002/*4601	B61/B46	*0304/*0801	Cw10/Cw8
HT49	*2402/*2402	A24/A24	*5201/*5201	B52/B52	*1202/*1202	Blank/blank
HT50	*2601/*3303	A26/A33	*4002/*5101	B61/B51	*0304/*1402	Cw10/Cw1/blank
HT51	*1101/*3101	A11/A31	*4801/*5101	B48/B51	*0801/*1402	Cw8/Cw1/blank
HT52	*2402/*2402	A24/A24	*4001/*4006	B60/B61	*0304/*0801	Cw10/Cw8
HT53	*1101/*1101	A11/A11	*5603/*670101	B56/B67	*0102/*0702	Cw1/Cw7
HT54	*1101/*2601	A11/A26	*0702/*4801	B7/B48	*0702/*0801	Cw7/Cw8
HT55	*2402/*2402	A24/A24	*4002/*4601	B61/B46	*0102/*0304	Cw1/Cw10
HT56	*0201/*0201	A2/A2	*4002/*5101	B61/B51	*0303/*1402	Cw9/Cw1/blank
HT57	*2603/*3303	A26/A33	*1501/*440301	B62/B44	*0303/*1403	Cw9/Cw1/blank
HT60	*0201/*1101	A2/A11	*3501/*4801	B35/B48	*0303/*0801	Cw9/Cw8

HT\_33 はゲノム DNA の保存状況が悪く解析が不可能であった。

表 2-2-B 本研究における DILI 患者の HLA クラス II 遺伝子座の解析結果 (52 症例, 104 アリル)

Sample	HLA-DRB1 遺伝子		HLA-DQB1 遺伝子		HLA-DPB1 遺伝子	
	遺伝子型	セロタイプ	遺伝子型	セロタイプ	遺伝子型	セロタイプ
HT1	*1302/*1502	DR13/DR15	*0601/*0604	DQ6/DQ6	*0901/*0901	DQ6/DQ6
HT2	*0405/*1502	DR4/DR15	*0401/*0601	DQ4/DQ6	*0201/*0402	DQ4/DQ6
HT3	*1302/*1602	DR13/DR16	*0502/*0609	DQ5/DQ6	*0201/*0301	DQ5/DQ6
HT4	*0901/*1101	DR9/DR11	*0301/*0303	DQ7/DQ9	*0201/*0301	DQ7/DQ9
HT5	*0405/*1502	DR4/DR15	*0401/*0601	DQ4/DQ6	*0201/*0501	DQ4/DQ6
HT6	*0405/*0803	DR4/DR8	*0401/*0601	DQ4/DQ6	*0201/*0501	DQ4/DQ6
HT7	*0101/*0802	DR1/DR8	*0402/*0501	DQ4/DQ5	*0201/*0501	DQ4/DQ5
HT8	*0401/*1202	DR4/DR12	*0301/*0301	DQ7/DQ7	*0201/*1401	DQ7/DQ7
HT9	*0403/*0901	DR4/DR9	*0302/*0303	DQ8/DQ9	*0301/*0501	DQ8/DQ9
HT10	*0101/*1502	DR1/DR15	*0501/*0601	DQ5/DQ6	*0201/*0901	DQ5/DQ6
HT11	*0803/*1406	DR8/DR14	*0301/*0601	DQ7/DQ6	*0201/*0301	DQ7/DQ6
HT12	*0101/*1502	DR1/DR15	*0501/*0601	DQ5/DQ6	*0501/*0901	DQ5/DQ6
HT13	*0101/*0803	DR1/DR8	*0501/*0601	DQ5/DQ6	*0202/*0402	DQ5/DQ6
HT15	*0101/*1202	DR1/DR12	*0301/*0501	DQ7/DQ5	*0402/*0501	DQ7/DQ5
HT16	*0405/*0901	DR4/DR9	*0303/*0401	DQ9/DQ4	*0501/*0501	DQ9/DQ4
HT17	*1403/*1406	DR14/DR14	*0301/*0301	DQ7/DQ7	*0201/*0501	DQ7/DQ7
HT18	*0802/*0901	DR8/DR9	*0303/*0402	DQ9/DQ4	*0501/*0501	DQ9/DQ4
HT19	*0405/*0901	DR4/DR9	*0303/*0401	DQ9/DQ4	*0301/*0501	DQ9/DQ4
HT20	*0802/*1201	DR8/DR12	*0302/*0303	DQ8/DQ9	*0501/*0501	DQ8/DQ9

表 2-2-B (続き)

Sample	HLA-DRB1 遺伝子		HLA-DQB1 遺伝子		HLA-DPB1 遺伝子	
	遺伝子型	セロタイプ	遺伝子型	セロタイプ	遺伝子型	セロタイプ
HT21	*0405/*0802	DR4/DR8	*0302/*0401	DQ8/DQ4	*0501/*0501	
HT22	*0405/*0901	DR4/DR9	*0303/*0401	DQ9/DQ4	*0501/*3601	
HT23	*0406/*1101	DR4/DR11	*0301/*0302	DQ7/DQ8	*0201/*0202	
HT24	*0405/*1502	DR4/DR15	*0401/*0601	DQ4/DQ6	*0201/*0901	
HT25	*1202/*1502	DR12/DR15	*0301/*0601	DQ7/DQ6	*0201/*0901	
HT26	*0401/*1302	DR4/DR13	*0301/*0604	DQ7/DQ6	*0201/*1401	
HT27	*0405/*1201	DR4/DR12	*0301/*0401	DQ7/DQ4	*0501/*0501	
HT28	*0803/*0901	DR8/DR9	*0303/*0601	DQ9/DQ6	*0201/*0501	
HT29	*0803/*1201	DR8/DR12	*0301/*0601	DQ7/DQ6	*0201/*0501	
HT30	*1405/*1502	DR14/DR15	*0503/*0601	DQ5/DQ6	*0501/*0901	
HT31	*0901/*1401	DR9/DR14	*0303/*0503	DQ9/DQ5	*0201/*0301	
HT32	*1302/*1403	DR13/DR1403/DR14	*0301/*0604	DQ7/DQ6	*0201/*0401	
HT34	*0405/*0406	DR4/DR4	*0302/*0401	DQ8/DQ4	*0201/*0201	
HT35	*0405/*1502	DR4/DR15	*0401/*0601	DQ4/DQ6	*0301/*0901	
HT36	*0405/*1502	DR4/DR15	*0401/*0601	DQ4/DQ6	*0501/*0901	
HT37	*1201/*1502	DR12/DR15	*0301/*0601	DQ7/DQ6	*0501/*0901	
HT38	*0901/*1502	DR9/DR15	*0303/*0601	DQ9/DQ6	*0501/*0901	
HT40	*0803/*1501	DR8/DR15	*0601/*0602	DQ6/DQ6	*0501/*1901	
HT41	*0403/*0403	DR4/DR4	*0302/*0302	DQ8/DQ8	*0201/*0501	

表 2-2-B (続き)

Sample	HLA-DRB1 遺伝子		HLA-DQB1 遺伝子		HLA-DPB1 遺伝子	
	遺伝子型	セロタイプ	遺伝子型	セロタイプ	遺伝子型	セロタイプ
HT42	*0403/*1501	DR4/DR15	*0302/*0602	DQ8/DQ6	*0501/*0501	
HT43	*0406/*0410	DR4/DR4	*0302/*0402	DQ8/DQ4	*0201/*0501	
HT44	*0401/*0802	DR4/DR8	*0301/*0402	DQ7/DQ4	*0201/*0301	
HT45	*1302/*1501	DR13/DR15	*0602/*0604	DQ6/DQ6	*0201/*0401	
HT47	*0803/*1405	DR8/DR14	*0503/*0601	DQ5/DQ6	*0501/*0501	
HT49	*1502/*1502	DR15/DR15	*0601/*0601	DQ6/DQ6	*0901/*0901	
HT50	*0405/*0803	DR4/DR8	*0401/*0601	DQ4/DQ6	*0301/*0501	
HT51	*0405/*0901	DR4/DR9	*0303/*0401	DQ9/DQ4	*0301/*0501	
HT52	*0405/*0410	DR4/DR4	*0401/*0402	DQ4/DQ4	*0301/*4701	
HT54	*0101/*1405	DR1/DR14	*0501/*0503	DQ5/DQ5	*0402/*0501	
HT55	*0803/*1501	DR8/DR15	*0601/*0602	DQ6/DQ6	*0202/*0501	
HT56	*1403/*1501	DR1403/DR14/DR15	*0301/*0602	DQ7/DQ6	*0501/*1401	
HT57	*1302/*1501	DR13/DR15	*0602/*0604	DQ6/DQ6	*0901/*1301	
HT60	*0406/*0802	DR4/DR8	*0302/*0302	DQ8/DQ8	*0201/*0501	

HT\_33、HT\_53 はゲノム DNA の保存状況が悪く解析が不可能であった。

表 2-3-A DILI 患者の HLA クラス I 遺伝子のアレル頻度分布

アレル	HLA-A				HLA-B				HLA-Cw						
	N	頻度[95%CI] (%)	対照(%)	アレル	N	頻度[95%CI] (%)	対照(%)	アレル	N	頻度[95%CI] (%)	対照(%)	アレル	N	頻度[95%CI] (%)	対照(%)
*0101	1	0.94 [0.00-2.78]	0.57	*0702	7	6.60 [1.88-11.3]	3.63	*0102	12	11.3 [5.29-17.4]	16.6				
*0201	8	7.55 [2.52-12.6]	10.71	*1501	4	3.77 [0.15-7.40]	9.37	*0302	2	1.89 [0.00-4.48]	0.19				
*0206	7	6.60 [1.88-11.3]	8.99	*1511	2	1.89 [0.00-4.48]	0.96	*0303	15	14.2 [7.52-20.8]	13.2				
*0207	3	2.83 [0.00-5.99]	2.87	*1518	4	3.77 [0.15-7.40]	1.72	*0304	14	13.2 [6.76-19.7]	13.8				
*0210	1	0.94 [0.00-2.78]	0.76	*2704	1	0.94 [0.00-2.78]	0.38	*0401	2	1.89 [0.00-4.48]	4.40				
*0301	1	0.94 [0.00-2.78]	0.57	*2705	1	0.94 [0.00-2.78]	↑	*0501	1	0.94 [0.00-2.78]	0.38				
*1101	11	10.4 [4.57-16.2]	10.71	*3501	9	8.49 [3.18-13.8]	8.80	*0702	11	10.4 [4.57-16.2]	10.3				
*2402	42	39.6 [30.3-48.9]	36.5	*3901	1	0.94 [0.00-2.78]	4.02	*0704	3	2.83 [0.00-5.99]	1.34				
*2601	9	8.49 [3.18-13.8]	11.3	*4001	6	5.66 [1.26-10.1]	5.35	*0801	13	12.3 [6.02-18.5]	9.75				
*2602	3	2.83 [0.00-5.99]	N.R.	*4002	9	8.49 [3.18-13.8]	8.41	*0803	2	1.89 [0.00-4.48]	1.34				
*2603	2	1.89 [0.00-4.48]	1.91	*4006	5	4.72 [0.68-8.75]	4.78	*1202	16	15.1 [8.28-21.9]	11.1				
*3101	10	9.43 [3.87-15.0]	6.88	*4402	1	0.94 [0.00-2.78]	0.38	*1402	9	8.49 [3.18-13.8]	4.78				
*3303	8	7.55 [2.52-12.6]	7.84	*4403	1	0.94 [0.00-2.78]	6.69	*1403	5	4.72 [0.68-8.75]	7.07				
				*440301	4	3.77 [0.15-7.40]	↑	*1502	1	0.94 [0.00-2.78]	4.40				
				*4601	4	3.77 [0.15-7.40]	3.44								
				*4801	6	5.66 [1.26-10.1]	5.54								
				*5101	11	10.38 [4.57-16.2]	6.88								
				*5201	15	14.15 [7.52-20.8]	10.9								
				*5401	2	1.89 [0.00-4.48]	7.07								

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*5502	2	1.89 [0.00-4.48]	2.87
*5504	1	0.94 [0.00-2.78]	0.38
*5601	3	2.83 [0.00-5.99]	0.38
*5603	1	0.94 [0.00-2.78]	0.57
*5801	2	1.89 [0.00-4.48]	0.19
*5901	1	0.94 [0.00-2.78]	1.72
*6701	1	0.94 [0.00-2.78]	0.76
*670101	2	1.89 [0.00-4.48]	↑

対照群のアリル頻度は、Nakajima F. et al., Analysis of HLA haplotypes in Japanese, using high resolution allele typing, MHC Vol. 8(1): 1-32, 2008 から引用した。  
 N. R.: 報告無し、↑: 上に含まれる。

表 2-3-B DILI 患者の HLA クラス II 遺伝子のアレル頻度分布

アレル	HLA-DRB1			HLA-DQB1			HLA-DPB1				
	N	頻度[95%CI] (%)	対照(%)	アレル	N	頻度[95%CI] (%)	対照(%)	アレル	N	頻度[95%CI] (%)	対照(%)
*0101	6	5.77 [1.29-10.3]	3.88	*0301	16	15.4 [8.45-22.3]	12.0	*0201	25	24.0 [15.8-32.3]	26.5
*0401	3	2.88 [0.00-6.10]	1.36	*0302	11	10.6 [4.67-16.5]	10.1	*0202	3	2.88 [0.00-6.10]	3.51
*0403	4	3.85 [0.15-7.54]	3.88	*0303	11	10.6 [4.67-16.5]	14.5	*0301	11	10.6 [4.67-16.5]	5.17
*0405	15	14.4 [7.67-21.2]	13.2	*0401	15	14.4 [7.67-21.2]	13.0	*0401	2	1.92 [0.00-4.56]	3.93
*0406	4	3.85 [0.15-7.54]	3.49	*0402	5	4.81 [0.70-8.92]	3.88	*0402	4	3.85 [0.15-7.54]	5.79
*0410	2	1.92 [0.00-4.56]	2.13	*0501	6	5.77 [1.29-10.3]	4.46	*0501	38	36.5 [27.3-45.8]	40.7
*0802	6	5.77 [1.29-10.3]	3.49	*0502	1	0.96 [0.00-2.84]	3.29	*0901	14	13.5 [6.90-20.0]	7.23
*0803	9	8.65 [3.25-14.1]	6.40	*0503	4	3.85 [0.15-7.54]	5.43	*1301	1	0.96 [0.00-2.84]	1.65
*0901	10	9.62 [3.95-15.3]	13.8	*0601	23	22.1 [14.1-30.1]	14.9	*1401	3	2.88 [0.00-6.10]	2.07
*1101	2	1.92 [0.00-4.56]	3.68	*0602	6	5.77 [1.29-10.3]	11.6	*1901	1	0.96 [0.00-2.84]	0.62
*1201	4	3.85 [0.15-7.54]	2.52	*0604	5	4.81 [0.70-8.92]	5.43	*3601	1	0.96 [0.00-2.84]	N.R.
*1202	3	2.88 [0.00-6.10]	2.13	*0609	1	0.96 [0.00-2.84]	0.19	*4701	1	0.96 [0.00-2.84]	0.21
*1302	6	5.77 [1.29-10.3]	5.62								
*1401	1	0.96 [0.00-2.84]	4.26								
*1403	3	2.88 [0.00-6.10]	0.78								
*1405	3	2.88 [0.00-6.10]	3.10								
*1406	2	1.92 [0.00-4.56]	2.13								
*1501	6	5.77 [1.29-10.3]	11.6								
*1502	14	13.5 [6.90-20.0]	8.91								
*1602	1	0.96 [0.00-2.84]	0.78								

添付資料 2-4

対照群のアリル頻度は、Nakajima F. et al., Analysis of HLA haplotypes in Japanese, using high resolution allele typing, MHC Vol. 8(1): 1-32, 2008 から引用した。

N. R.: 報告無し



## 添付資料2-5

## SNP Array 6.0 による遺伝子解析結果

No.	受付 ID	Runnig ID	Genotyping result			
			濃度(ng/μl)	調整後濃度	cQC	QC
1	Hepatotoxicity_2	2220001A01	80.9	53.9	2.24	97.65
2	Hepatotoxicity_3	2220001A02	105.1	52.6	2.04	95.20
3	Hepatotoxicity_6	2220001A03	80.0	53.3	2.38	97.29
4	Hepatotoxicity_7	2220001A04	82.9	51.8	2.51	97.82
5	Hepatotoxicity_10	2220001A05	66.2	53.8	2.69	98.87
6	Hepatotoxicity_12	2220001A06	94.1	52.3	2.36	98.25
7	Hepatotoxicity_13	2220001A07	103.9	52.0	1.93	95.93
8	Hepatotoxicity_15	2220001A08	55.9	55.9	1.94	96.59
9	Hepatotoxicity_16	2220001A09	46.1	46.1	1.83	97.32
10	Hepatotoxicity_17	2220001A10	45.2	45.2	1.72	97.52
11	Hepatotoxicity_18	2220001A11	148.1	52.3	2.33	98.31
12	Hepatotoxicity_19	2220001A12	177.8	52.3	2.16	98.01
13	Hepatotoxicity_20	2220001B01	89.9	52.9	2.15	97.35
14	Hepatotoxicity_21	2220001B02	212.8	53.2	1.53	96.43
15	Hepatotoxicity_22	2220001B03	69.3	52.0	1.56	94.94
16	Hepatotoxicity_23	2220001B04	180.5	53.1	1.78	97.35
17	Hepatotoxicity_24	2220001B05	116.5	51.8	2.27	97.85
18	Hepatotoxicity_25	2220001B06	52.7	52.7	1.86	95.20
19	Hepatotoxicity_26	2220001B07	113.7	53.5	1.85	96.82
20	Hepatotoxicity_27	2220001B08	45.3	45.3	2.19	98.38
21	Hepatotoxicity_31	2220001B09	45.8	45.8	1.84	97.42
22	Hepatotoxicity_32	2220001B10	55.5	55.5	1.67	94.11
23	Hepatotoxicity_35	2220001B11	154.7	51.6	1.91	97.05
24	Hepatotoxicity_36	2220001B12	81.9	51.2	1.24	97.15
25	Hepatotoxicity_38	2220001C01	158.4	52.8	2.53	98.78
26	Hepatotoxicity_39	2220001C02	88.6	52.1	2.88	98.94
27	Hepatotoxicity_40	2220001C03	81.0	52.4	2.83	98.81
28	Hepatotoxicity_41	2220001C04	92.8	51.6	2.82	98.78
29	Hepatotoxicity_42	2220001C05	125.5	51.7	2.69	99.07
30	Hepatotoxicity_43	2220001C06	55.2	55.2	2.48	97.55
31	Hepatotoxicity_44	2220001C07	81.0	52.4	2.59	99.21
32	Hepatotoxicity_45	2220001C08	64.3	52.2	2.15	97.12
33	Hepatotoxicity_47	2220001C09	69.0	51.8	2.04	98.05
34	Hepatotoxicity_49	2220001C10	54.0	54.0	0.77	90.70
35	Hepatotoxicity_51	2220001C11	54.3	54.3	1.97	96.46
36	Hepatotoxicity_52	2220001C12	58.3	51.4	0.15	87.29
37	Hepatotoxicity_54	2220001D01	56.6	53.1	2.51	98.54
38	Hepatotoxicity_60	2220001D02	297.2	52.4	2.13	97.72
39	Hepatotoxicity_61	2220001D03	81.7	52.9	2.34	98.11
40	Hepatotoxicity_62	2220001D04	103.9	52.0	2.30	98.97
41	Hepatotoxicity_63	2220001D05	60.1	52.0	3.00	98.38
42	Hepatotoxicity_65	2220001D06	114.1	53.7	1.81	95.83
43	Hepatotoxicity_4	2220001D07	38.2	38.2	2.98	98.74
44	Hepatotoxicity_50	2220001D08	43.8	43.8	2.73	98.68
45	Hepatotoxicity_67	2220001D09	37.7	37.7	2.46	98.81
46	Hepatotoxicity_9	2220002A01	39.3	39.3	2.89	98.28
47	Hepatotoxicity_5	2220003A01	29.1	29.1	2.53	97.42
48	Hepatotoxicity_8	2220003A02	32.7	32.7	3.13	98.94

GWAS実施時のFiltering Parameter: 本研究においてはFiltering parameter 3を採用した。

filtering parameter 1

SNP call rate	>95%	Case, Control
HWE	>0.1%	Control
MAF	>1%	Case, Control

pj222(48) vs pj304(184)  
Filter passed:

A vs B p # remaining SNP	observed/expected	614,563	SNPs
< 0.05	32,548	1,059	
< 0.01	7,457	1,213	
< 10 <sup>-3</sup>	1431	2,328	
< 10 <sup>-4</sup>	557	9,063	
< 10 <sup>-5</sup>	354	57,602	
< 10 <sup>-6</sup>	245	398,657	

pj222(48) vs pj304(184)\*  
Filter passed:

A vs B p # remaining SNP	observed/expected	599,507	SNPs
< 0.05	31,485	1,050	
< 0.01	7,056	1,177	
< 10 <sup>-3</sup>	1237	2,063	
< 10 <sup>-4</sup>	442	7,373	
< 10 <sup>-5</sup>	255	42,535	
< 10 <sup>-6</sup>	184	306,919	

\* Add pj208 (87sample) in genotyping with GTC v4

filtering parameter 2

SNP call rate	>95%	Case, Control
HWE	>0.1% <td>Control</td>	Control
MAF	>10% <td>Case, Control</td>	Case, Control

pj222(48) vs pj304(184)  
Filter passed:

A vs B p # remaining SNP	observed/expected	457,706	SNPs
< 0.05	23,543	1,029	
< 0.01	5,484	1,198	
< 10 <sup>-3</sup>	1103	2,410	
< 10 <sup>-4</sup>	477	10,422	
< 10 <sup>-5</sup>	317	69,258	
< 10 <sup>-6</sup>	219	478,473	

pj222(48) vs pj304(184)\*  
Filter passed:

A vs B p # remaining SNP	observed/expected	445,762	SNPs
< 0.05	22,665	1,017	
< 0.01	5,134	1,152	
< 10 <sup>-3</sup>	912	2,046	
< 10 <sup>-4</sup>	359	8,054	
< 10 <sup>-5</sup>	221	49,578	
< 10 <sup>-6</sup>	161	361,179	

\* Add pj208 (87sample) in genotyping with GTC v4

filtering parameter 3

SNP call rate	>95%	Case, Control
HWE	>0.1%, >10 <sup>^(-8)</sup> * <td>Control, case</td>	Control, case
MAF	>1% <td>Case, Control</td>	Case, Control

\* HWEp < 10<sup>^(-8)</sup>: 330/368 SNPs ... errors in scatter

pj222(48) vs pj304(184)\*\*  
Filter passed:

A vs B p # remaining SNP	observed/expected	596,345	SNPs
< 0.05	30,110	1,010	
< 0.01	6,146	1,031	
< 10 <sup>-3</sup>	683	1,145	
< 10 <sup>-4</sup>	74	1,241	
< 10 <sup>-5</sup>	3	0,503	
< 10 <sup>-6</sup>	0	0,000	

\*\* Add pj208 (87sample) in genotyping with GTC v4

29/74 SNPs  
... errors in scatter



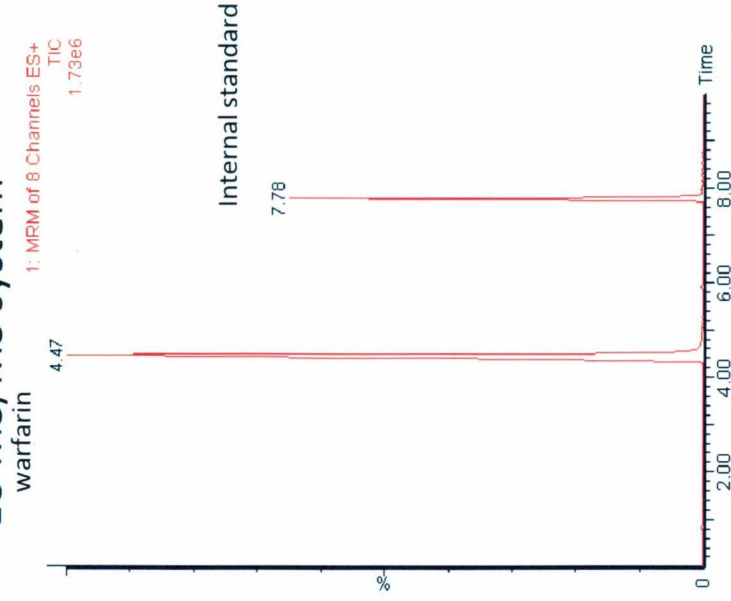
GWASによりP<0.0001で有意であったSNPsの一覧：22遺伝子上の45SNPsが見出された。

SNP ID	dbSNP RS ID	Chromosome	Physical Position	mAF	p-value	p-value	OR	95%CI-Low	High	AA	AB	BB	NoCall	AA	AB	BB	NoCall	AB	BB	Gene	annotation	SNP type	
*****	*****	*****	192558596	0.174589	0.7048	1.711E-05	3.03	1.80	5.11	4	23	21	21	0	4	23	21	4	42	0	CDS	sSNP	
*****	*****	*****	192559099	0.174569	0.7048	1.711E-05	0.33	0.20	0.56	21	23	4	4	0	138	23	4	138	42	0	intron	ISNP	
*****	*****	*****	182315890	0.5	0.0979	3.695E-05	2.68	1.66	3.88	17	22	4	4	0	43	22	4	43	80	0	upstream	gSNP	
*****	*****	*****	32312053	0.3987069	0.9902	0.0000906	2.46	1.55	3.88	17	21	10	10	0	23	21	10	23	84	0	intron	ISNP	
*****	*****	*****	88251350	0.3642241	0.4144	4.973E-05	2.54	1.60	4.01	12	28	8	8	0	21	28	8	21	75	0	upstream	gSNP	
*****	*****	*****	16709060	0.3484848	0.4768	8.169E-05	0.40	0.25	0.64	10	25	12	12	0	87	25	12	87	82	0	intron	ISNP	
*****	*****	*****	32025519	0.4396552	0.9571	3.965E-05	2.59	1.63	4.12	19	22	7	7	0	28	22	7	28	88	0	intron	ISNP	
*****	*****	*****	32027557	0.4375	0.9949	1.137E-05	0.33	0.20	0.55	1	21	26	26	0	44	21	26	44	92	0	intron	ISNP	
*****	*****	*****	54536388	0.2090517	0.5736	7.124E-06	0.33	0.20	0.54	18	24	6	6	0	127	24	6	127	53	0	downstream	gSNP	
*****	*****	*****	54712451	0.112069	0.2286	4.427E-05	3.35	1.83	6.13	2	18	28	28	0	0	30	28	0	30	154	0	downstream	gSNP
*****	*****	*****	54718848	0.1091703	0.2429	6.794E-05	3.32	1.79	6.15	2	17	28	28	1	0	29	28	1	29	153	2	downstream	gSNP
*****	*****	*****	54723959	0.2270742	0.5199	2.597E-05	0.35	0.26	0.64	14	28	4	4	2	120	28	4	120	58	1	downstream	gSNP	
*****	*****	*****	124839601	0.3512931	0.3584	9.331E-05	0.41	0.26	0.64	12	22	14	14	2	91	22	14	91	73	0	downstream	gSNP	
*****	*****	*****	118334001	0.0736607	0.5008	8.299E-05	0.25	0.12	0.52	33	14	1	1	0	159	14	1	159	17	0	downstream	gSNP	
*****	*****	*****	21593298	0.478355	0.6341	8.675E-05	0.38	0.24	0.63	3	22	32	32	1	49	22	32	49	95	40	0	downstream	gSNP
*****	*****	*****	82467237	0.0775862	0.443	4.278E-05	3.95	1.97	7.95	1	15	32	32	0	1	17	32	1	17	166	0	upstream	gSNP
*****	*****	*****	82479892	0.0775862	0.443	4.278E-05	3.95	1.97	7.95	1	15	32	32	0	1	17	32	1	17	166	0	downstream	gSNP
*****	*****	*****	82483761	0.0775862	0.443	4.278E-05	4.06	2.02	8.16	1	15	31	31	1	166	15	31	166	17	1	0	downstream	gSNP
*****	*****	*****	82482616	0.0797414	0.5126	7.704E-05	3.74	1.88	7.47	1	15	32	32	0	1	18	32	1	18	165	0	upstream	gSNP
*****	*****	*****	120422475	0.2780172	0.297	5.985E-05	3.65	1.88	7.09	37	11	0	0	0	88	11	0	88	74	22	0	downstream	gSNP
*****	*****	*****	120438560	0.2780172	0.297	5.985E-05	0.27	0.14	0.53	0	11	37	37	0	22	11	37	22	74	88	0	downstream	gSNP
*****	*****	*****	120443158	0.2780172	0.297	5.985E-05	0.27	0.14	0.53	0	11	37	37	0	22	11	37	22	74	88	0	intron	ISNP
*****	*****	*****	97656872	0.2543103	0.4486	4.982E-05	0.25	0.12	0.51	0	9	39	39	0	14	9	39	14	81	89	0	downstream	gSNP
*****	*****	*****	106877684	0.3340517	0.4152	0.0000389	2.58	1.63	4.08	14	21	13	13	0	13	21	13	13	80	91	0	downstream	gSNP
*****	*****	*****	106896233	0.3275862	0.327	5.307E-05	0.39	0.25	0.62	14	20	14	14	0	92	20	14	92	80	12	0	intron	ISNP
*****	*****	*****	106896488	0.3275862	0.327	5.307E-05	0.39	0.25	0.62	14	20	14	14	0	92	20	14	92	80	12	0	intron	ISNP
*****	*****	*****	106897036	0.3275862	0.327	5.307E-05	0.39	0.25	0.62	14	20	14	14	0	92	20	14	92	80	12	0	intron	ISNP
*****	*****	*****	71730857	0.3103448	0.2011	9.143E-05	0.31	0.17	0.57	0	14	34	34	0	19	14	34	19	92	73	0	downstream	gSNP
*****	*****	*****	127448159	0.1717391	0.1323	4.511E-05	2.93	1.72	4.98	3	23	20	20	2	1	48	20	1	48	135	0	upstream	gSNP
*****	*****	*****	107277967	0.1349558	0.1334	5.037E-05	0.32	0.18	0.57	26	19	3	3	0	142	19	3	142	36	0	intron	ISNP	
*****	*****	*****	56870743	0.3685345	0.1011	9.976E-05	0.35	0.20	0.60	2	15	31	31	0	26	15	31	26	100	58	0	intron	ISNP
*****	*****	*****	56877712	0.3836207	0.2384	7.311E-05	0.35	0.21	0.60	2	16	30	30	0	30	16	30	30	98	56	0	intron	ISNP
*****	*****	*****	56885147	0.3469828	0.1093	8.606E-05	0.33	0.19	0.59	1	15	32	32	0	23	15	32	23	98	63	0	CDS	sSNP
*****	*****	*****	79112449	0.4978448	0.0508	8.014E-05	0.39	0.24	0.63	4	23	21	21	0	62	23	21	62	78	44	0	upstream	gSNP
*****	*****	*****	83739456	0.3900862	0.844	1.461E-05	0.31	0.18	0.54	0	19	29	29	0	35	19	29	35	92	57	0	upstream	gSNP
*****	*****	*****	29853048	0.4267241	0.4586	7.912E-05	2.49	1.57	3.94	19	20	9	9	0	29	20	9	29	82	73	0	downstream	gSNP
*****	*****	*****	24056773	0.1190476	0.5776	0.0000418	0.30	0.17	0.55	26	21	1	1	0	153	21	1	153	28	2	1	upstream	gSNP
*****	*****	*****	56774371	0.4482759	0.0995	3.472E-05	2.62	1.65	4.17	17	27	4	4	0	24	27	4	24	99	61	0	downstream	gSNP
*****	*****	*****	56774901	0.4482759	0.0995	3.472E-05	0.38	0.24	0.61	4	27	17	17	0	61	27	17	61	99	24	0	upstream	gSNP
*****	*****	*****	5675093	0.4482759	0.0995	3.472E-05	2.62	1.65	4.17	17	27	4	4	0	24	27	4	24	99	61	0	downstream	gSNP
*****	*****	*****	56794076	0.45671	0.3574	0.0000749	0.39	0.25	0.63	4	26	17	17	1	67	26	17	67	83	34	0	downstream	gSNP
*****	*****	*****	45656760	0.1593886	0.0206	1.737E-05	0.32	0.19	0.55	23	21	4	4	0	143	21	4	143	86	6	3	upstream	gSNP
*****	*****	*****	16783629	0.4152174	0.290	4.728E-05	2.90	1.71	4.92	27	17	2	2	0	56	17	2	56	86	42	0	downstream	gSNP
*****	*****	*****	16801899	0.469697	0.2137	8.608E-05	2.59	1.60	4.21	25	18	5	5	0	47	18	5	47	83	53	1	upstream	gSNP

# LC-MS/MSによる血清中薬物の高感度分析



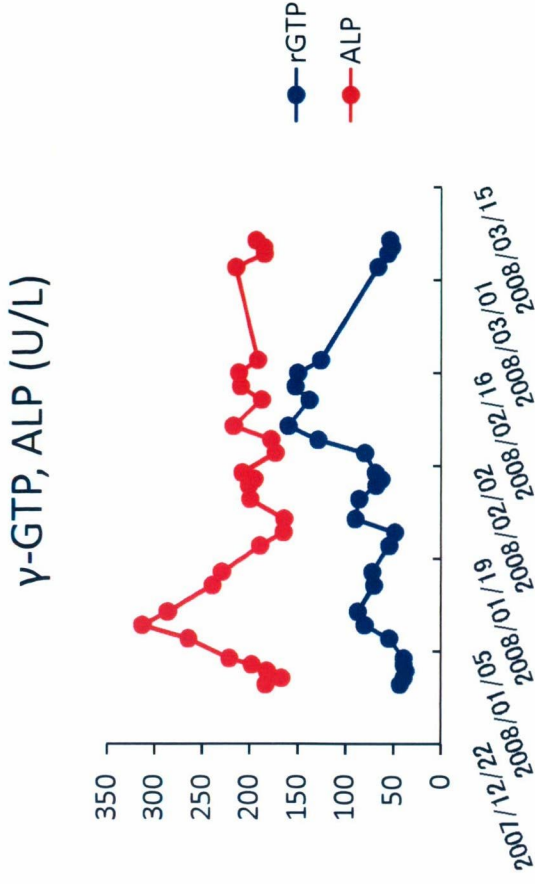
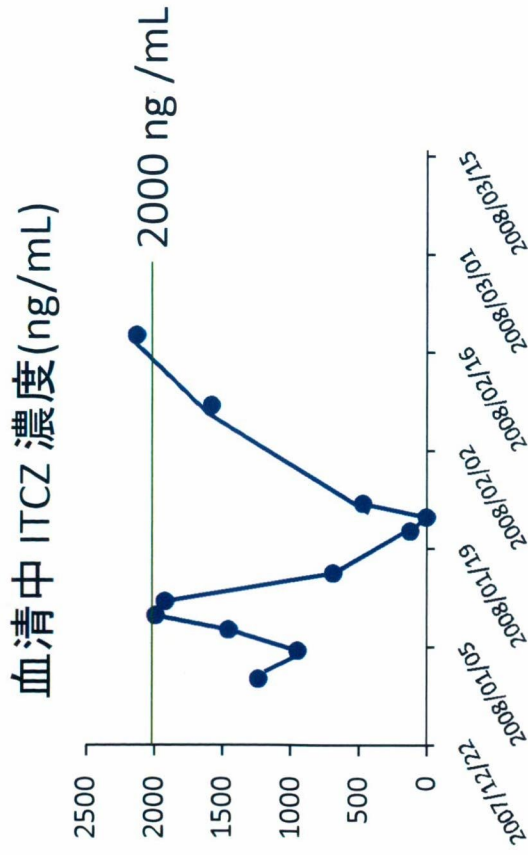
LC-MS/MS system



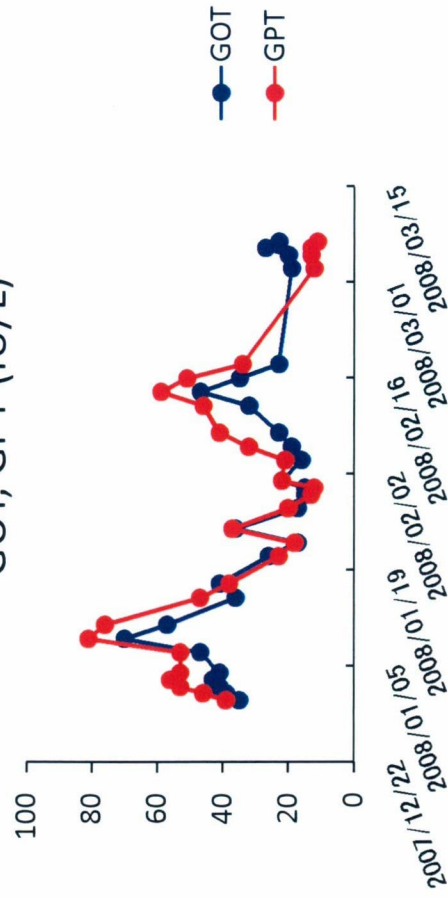
## LC-MS/MSによる定量系を確立した薬物

6-mercaptopurine	levofloxacin	warfarin	clarithromycin
acetaminophen	losartan	estrone	cyclosporin
acyclovir	lovastatin	estradiol	D-panthenol
allopurinol	loxoprofen	2-hydroxyestradiol	digoxin
ambroxol	methotrexate	2-methoxyestradiol	estramustine
azathiopurine	mianserin	bortezomib	estromustine
benzbromarone	minocycline	cilostazol	etizolam
brotizolam	mosapride	clomipramine	famotidine
canrenoic acid	nizatidine	felodipine	flosemide
carbamazepine	phenobarbital	glibenclamide	fluconazole
cefazolin	phenytoin	glimepiride	itraconazole
cefcapene pivoxil	piperacillin	imipramine	ketoconazole
cefdinir	pravastatin	loratadine	rosuvastatin
cefepime	prednisolone	midazolam	salbutamol
cefozoplan	promethazine	omeprazole	subactam
ceftriaxone	rabeprazole	propranolol	sulfamethoxazole
chlorpromazine	rebamipide	sertraline	sulfasarazine
voriconazole	lansoprazole	vancomycin	imipenem
tacrolimus	tosufloxacin	tolubtamide	vincristine
tazobactam	trimethoprim	meropenem	etoposide
thiopental	valproic acid	panipenem	ticlopidine
clopidogrel	gefitinibe	erlotinibe	

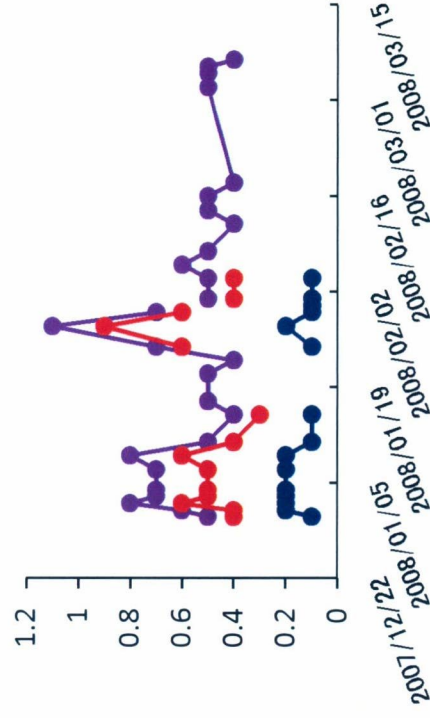
# ITCZ 誘発性 DILI 症例 (A) の ITCZ 濃度推移および肝検査値変動



GOT, GPT (IU/L)

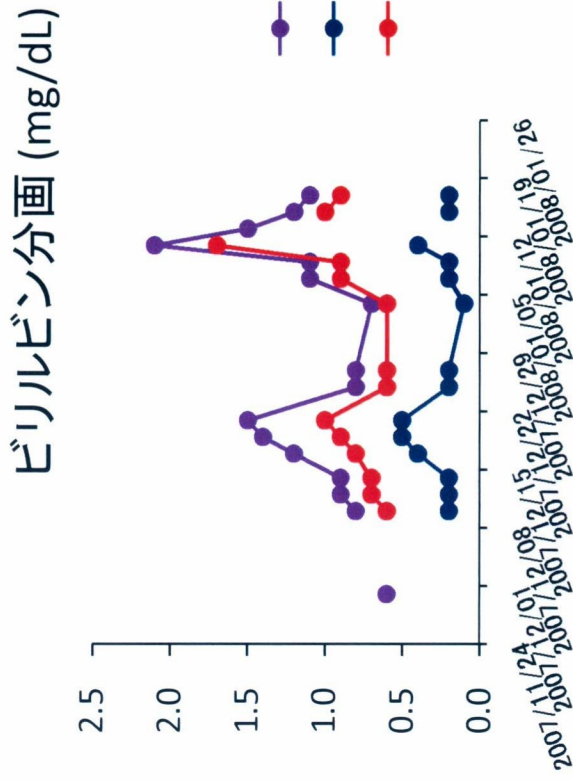
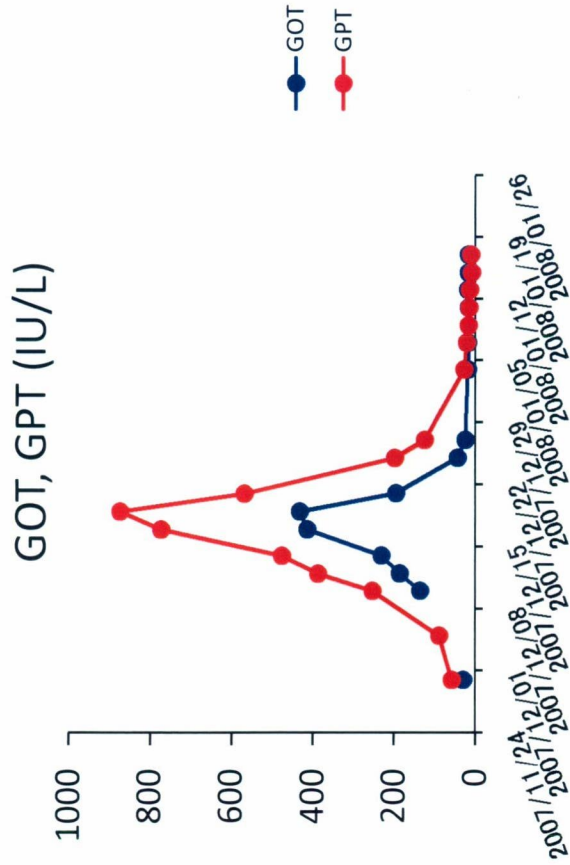
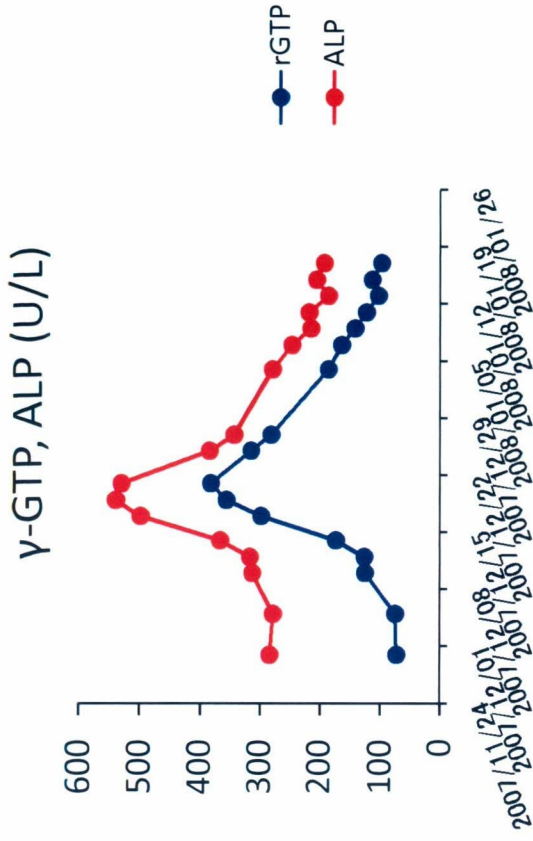
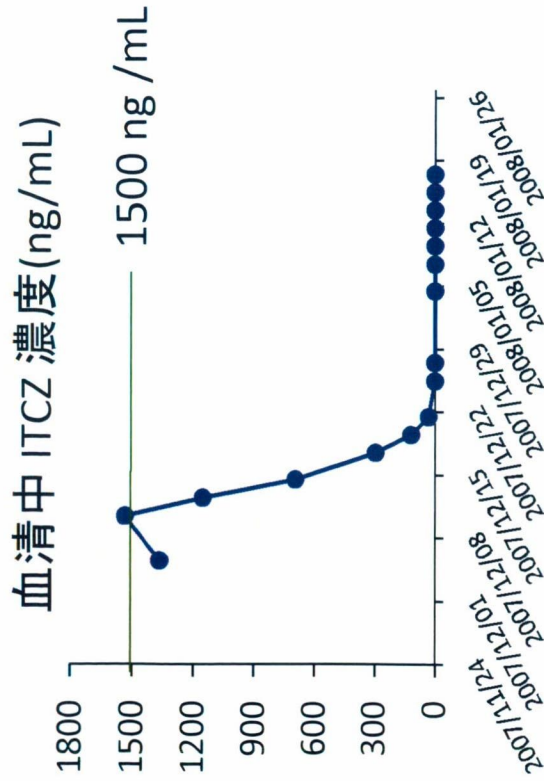


ビリルビン分画 (mg/dL)



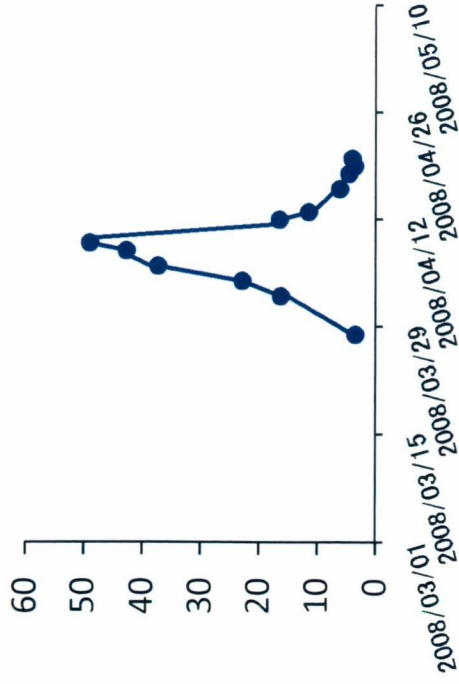


# ITCZ 誘発性 DILI 症例 (B) の ITCZ 濃度推移および肝検査値変動

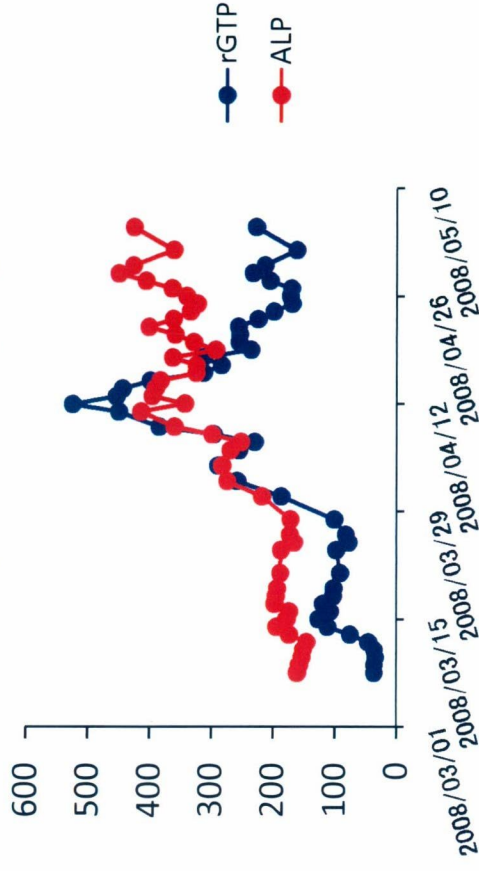


# ITCZ 誘発性 DILI 症例 (C) の ITCZ 濃度推移および肝検査値変動

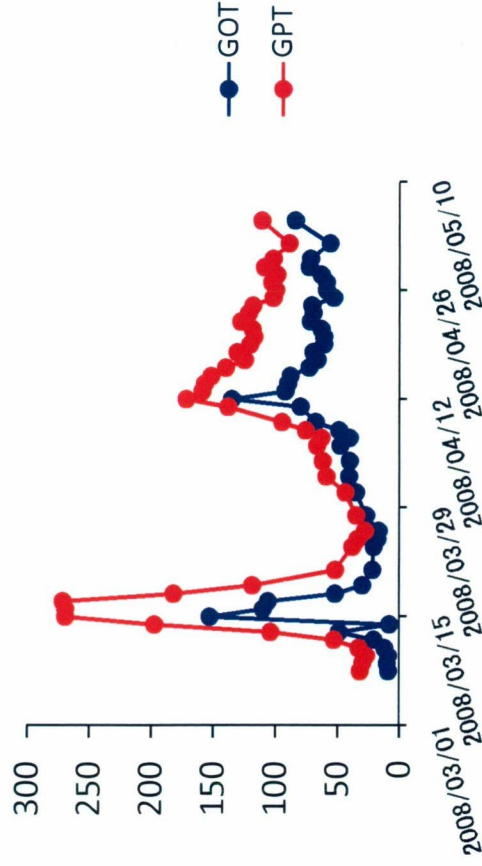
血清中 ITCZ 濃度 (ng/mL)



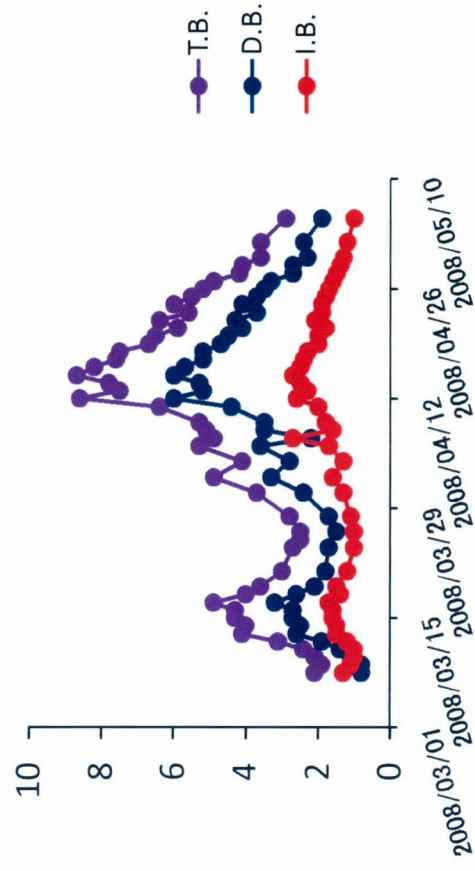
γ-GTP, ALP (U/L)



GOT, GPT (IU/L)

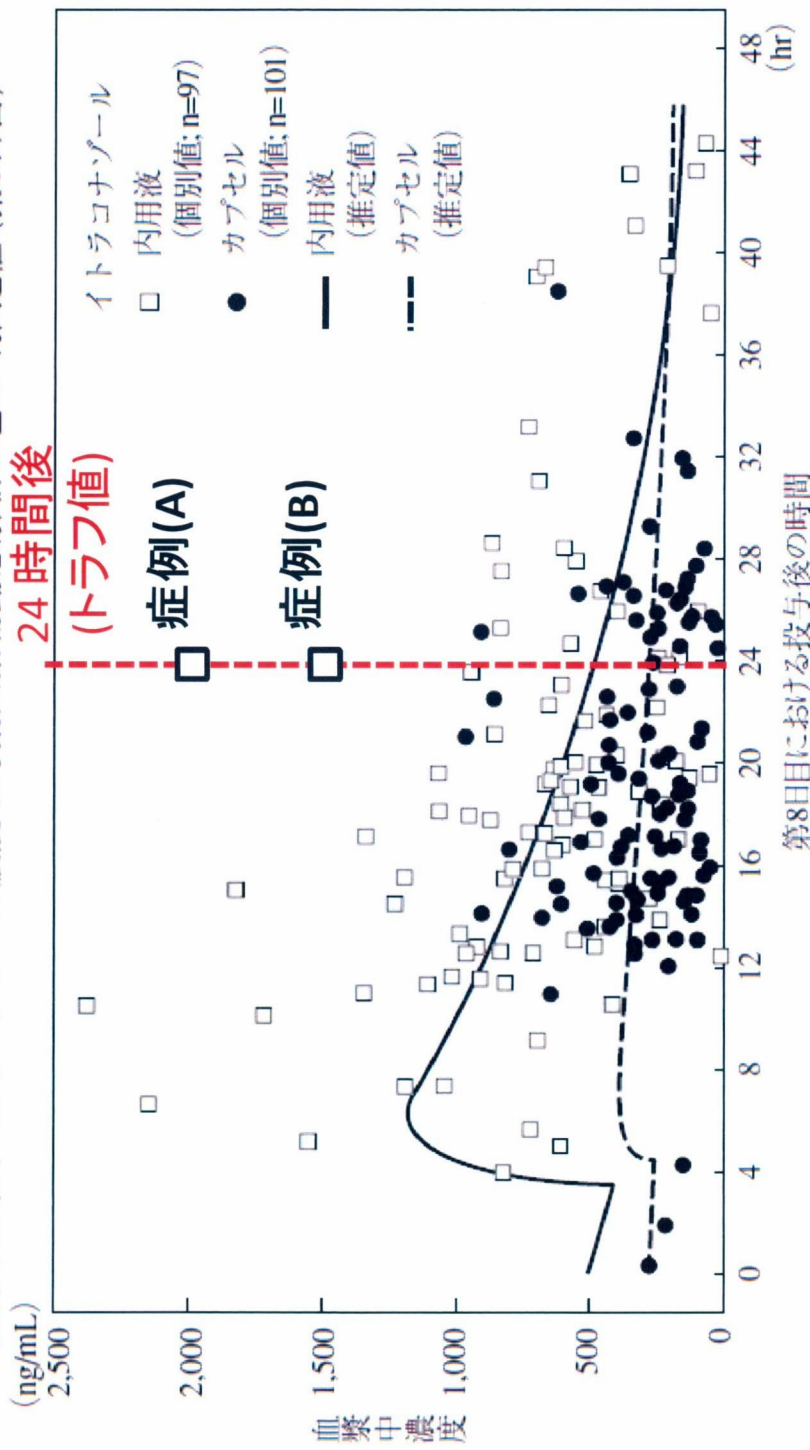


ビリルビン分画 (mg/dL)



# 症例(A)および(B)で認められたITCZ血清中濃度と標準的な体内動態推移との比較

個別の血漿中イトラコナゾール濃度と母集団薬物動態解析に基づく推定値 (第8日目)



山口 英世, 他: 日本化学療法学会雑誌, 2006

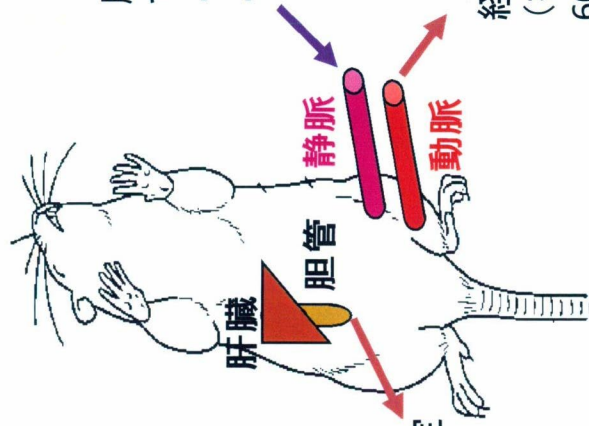
症例(A)および(B)において認められたトラフ濃度は一般的な日本人における体内動態推移よりも数倍高値であることがわかる。



# 胆汁流量、胆汁組成に対するイトラコナゾールの影響

## ラットを用いた検討

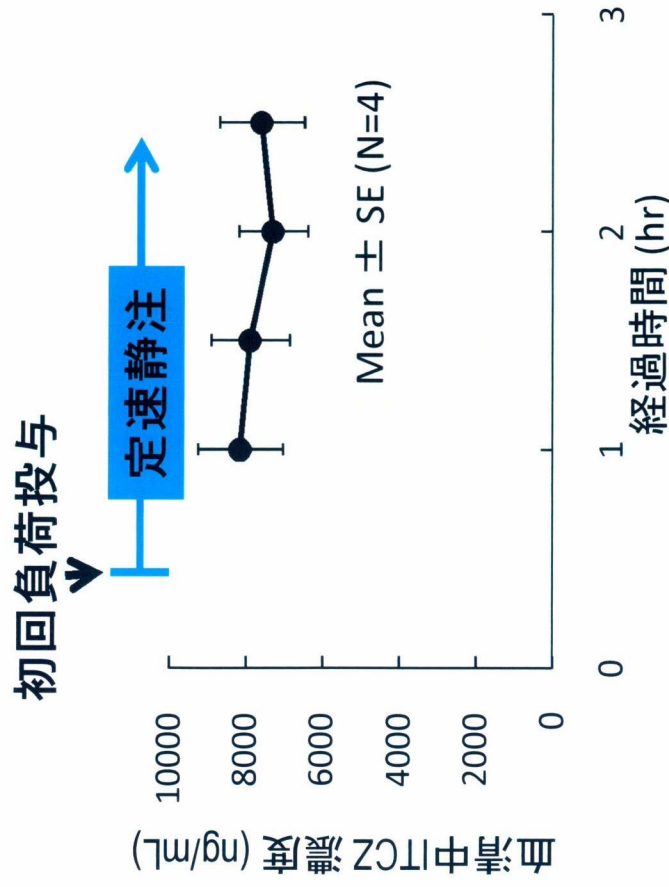
### 【実験方法】



胆汁採取開始後30min  
でITCZを静脈内投与  
・初回負荷量: 43mg/kg  
・維持量: 7.3mg/kg/hr

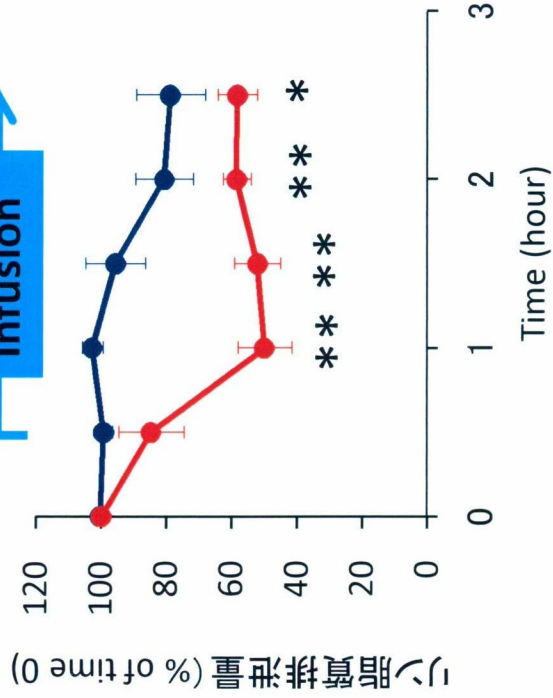
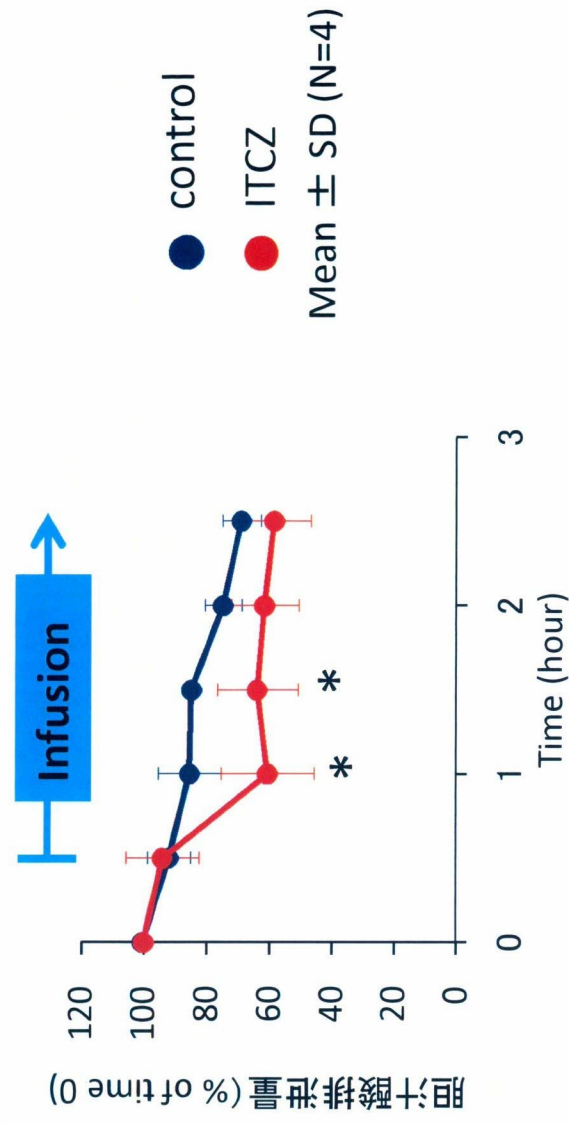
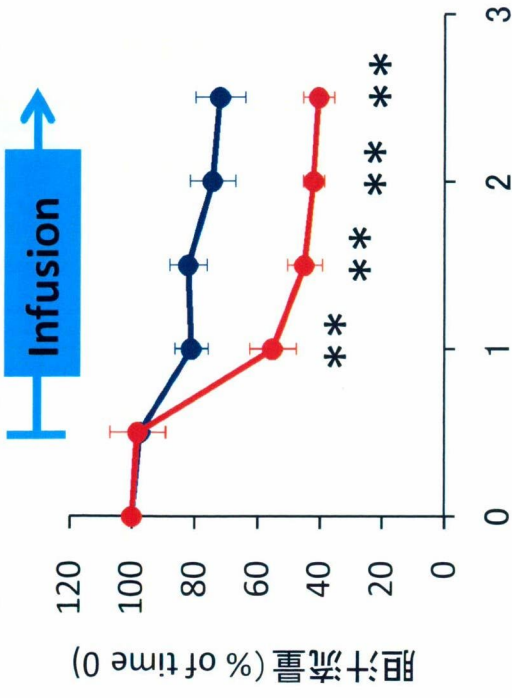
経時的に採血  
(投与開始後 30,  
60, 90, 120分後)

- ・胆汁流量測定
- ・胆汁回収



ラットをウレタンで麻酔後、大腿動静脈および胆管にカニキュレーションを施した。胆汁採取開始から30min後にITCZを投与し、ITCZ投与から2hr まで経時的に採血、胆汁流量測定および胆汁採取を行った。血清中ITCZ濃度はLC-MS/MSにより測定した。胆汁中の総胆汁酸濃度およびビリルビン脂質濃度は和光純薬より購入した測定キットを使用して測定した。

# 胆汁分泌に対するITCZの影響



ITCZは胆汁酸よりもリン脂質の胆汁への排泄を強く阻害した。

# hABCB4発現系を用いたホスファチジルコリン(PC)排出実験

Day 0

Day 2

Day 3

細胞継代

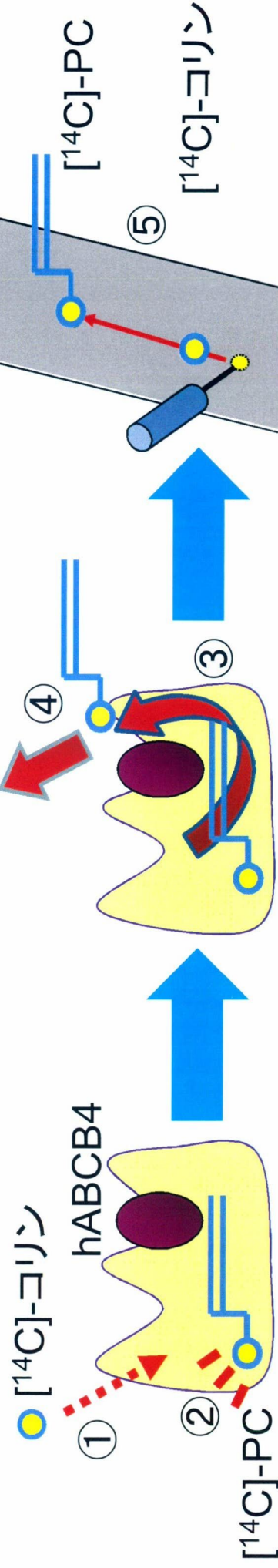
組み換えアデノウイルス  
(hMDR3)の感染

PC排出実験



wash [14C]-コリンの添加 タウロコロール酸の添加

タウロコロール酸(PCのアクセプター)



① コリンの添加

② 細胞内でPCに変換

③ hABCB4による細胞膜外側への反転

④ タウロコロール酸による引き抜き

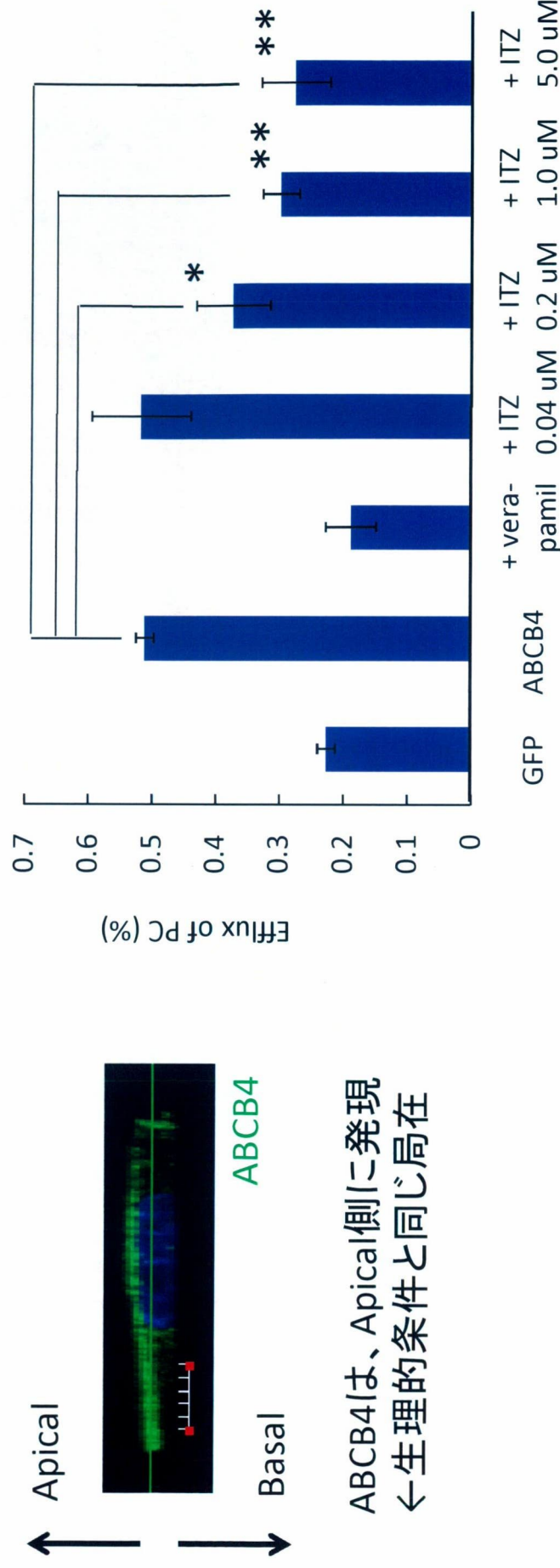
⑤ 薄層クロマトグラフィーによる分離、定量

hABCB4を発現させた細胞に、[14C]-コリンを加え、細胞内に取り込まれ[14C]-PCに変換され再び細胞外に排出された量を測定することで、hABCB4の機能を評価した。



# リン脂質排出ポンプ(ABCB4)に対するイトラコナゾールの影響

## - In vitro 実験系(ヒトABCB4 cDNA導入細胞)を用いた検討 -



ABCB4は、Apical側に発現  
←生理的条件と同じ局在

ITCZはABCB4によるリン脂質(PC)の輸送を用量依存的に阻害した。その阻害効果は今回のin vivo 実験において得られた濃度範囲内(0.2μM)においても観察された。