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Susumu Saito · Aritoshi Iida · Akihiro Sekine
Saori Kawauchi · Shoko Higuchi · Chie Ogawa
Yusuke Nakamura

Catalog of 680 variations among eight cytochrome P450 (*CYP*) genes, nine esterase genes, and two other genes in the Japanese population

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Abstract We screened DNAs from 48 Japanese individuals for single-nucleotide polymorphisms (SNPs) in eight cytochrome P450 (*CYP*) genes, nine esterase genes, and two other genes by directly sequencing the relevant genomic regions in their entirety except for repetitive elements. This approach identified 607 SNPs and 73 insertion/deletion polymorphisms among the 19 genes examined. Of the 607 SNPs, 284 were identified in *CYP* genes, 302 in esterase genes, and 21 in the other two genes (*GGT1*, and *TGM1*); overall, 37 SNPs were located in 5' flanking regions, 496 in introns, 55 in exons, and 19 in 3' flanking regions. These variants should contribute to studies designed to investigate possible correlations between genotypes and phenotypes of disease susceptibility or responsiveness to drug therapy.

Keywords Single-nucleotide polymorphism (SNP) · Cytochrome P450 (CYP) · Esterase · GGT1 · TGM1

Introduction

Cytochrome P450 (CYP) enzymes, many of which can catalyze xenobiotic compounds, constitute a superfamily of hemoproteins (Ding and Kaminsky 2003). *CYP* genes are classified into families and subfamilies on the basis of sequence similarities, and among them, numerous polymorphisms have been previously reported [Human Cytochrome P450 (*CYP*) Allele Nomenclature Committee, http://www.imm.ki.se/CYPalleles/]. The products of these and the other eleven genes selected for the work reported here are described in the following paragraphs.

CYP2A6 is a major player in the oxidation of nicotine and coumarin in human liver microsomes (Nakajima et al. 1996a; 1996b). Polymorphisms of *CYP2A6* that might affect enzymatic activity (Ariyoshi et al. 2001; Kitagawa et al. 2001; Pitarque et al. 2001; Daigo et al. 2002; Oscarson et al. 2002; Xu et al. 2002) or susceptibility to lung cancer (Pianezza et al. 1998; London et al. 1999; Miyamoto et al. 1999) have been reported. However, some of those variants may be rare substitutions or limited to specific ethnic groups (Kitagawa et al. 2001; Oscarson et al. 1999, 2002; Xu et al. 2002).

CYP2A13 may play important roles in xenobiotic toxicity and tobacco-related tumorigenesis in the respiratory tract (Su et al. 2000). Zhang et al. (2002) have identified a C-to-T polymorphism (Arg257Cys) in exon 5 of the gene, and the product of this variant is 37% to 56% less active than the wild-type protein toward all substrates tested.

CYP2B6 is involved in the metabolism of several clinically important drugs (Ekins and Wrighton 1999). Lang et al. (2001) have identified five polymorphisms that would affect amino acid sequences; among them, a C-to-T polymorphism (Arg487Cys) in exon 9 of the gene appears to be associated with enzymatic activity. However, some of those five variants could also be rare substitutions or limited to specific ethnic groups (Hiratsuka et al. 2002).

CYP2E catalyzes the conversion of ethanol to acetaldehyde and to acetate and also metabolizes the premutagenic nitrosamines present in cigarette smoke (Guengerich et al. 1991). Polymorphisms have been associated with increased risk of alcohol-related liver disease (Tanaka et al. 1997; Sun et al. 1999), lung cancer

S. Saito · A. Iida · A. Sekine · S. Kawauchi · S. Higuchi
Y. Nakamura
Laboratory for Genotyping, SNP Research Center,
Institute of Physical and Chemical Research,
Yokohama Institute, 1-7-22 Suehiro-cho, Tsurumi-ku,
Yokohama 230-0045, Japan

C. Ogawa · Y. Nakamura (✉)
Laboratory of Molecular Medicine, Human Genome Center,
Institute of Medical Science, University of Tokyo,
4-6-1 Shirokanedai, Minato-ku, Tokyo 108-8639, Japan
E-mail: yusuke@ims.u-tokyo.ac.jp
Tel.: +81-3-54495372
Fax: +81-3-54495433

Table 1 Accession numbers for the genomic and cDNA sequences used in this study

Gene name	Chromosomal localization	Accession no.					
		Genomic sequence			cDNA sequence		
CYP							
CYP2A6	19q13.2	NG_000008.2			NM_000762.3		
CYP2A13	19q13.2	AC008962.9			NM_000766.2		
CYP2B6	19q13.2	NG_000010.1			NM_000767.3		
CYP2E	10q24.3-qter	AL161645.14			NM_000773.2		
CYP2S1	19q13.1	NG_000011.1			NM_030622.2		
TBXAS1	7q34-q35	AC006021.2	AC004914.1	AC004961.2	XM_034816.1		
CYP7A1	8q11-q12	AC020782.10			XM_044651.1		
CYP7B1	8q21.3	AF127089.1	AF215845.2	AF176800.1	NM_004820.2		
Esterase							
AADAC	3q21.3-q25.2	AC068647.4			L32179.1		
CEL	9q34.3	AL138750.8	AL162417.20	AF072711.1	NM_001807.1		
CES1	16q13-q22.1	AC007602.4			L07764.1		
CES2	16q21	AC027131.4			XM_043817.1		
ESD	13q14.1-q14.2	AL136958.9			AF112219.1		
GZMA	5q11-q12	AC091977.1			NM_006144.2		
GZMB	14q11.2	AL136018.3			XM_12328.3	XM_032600.1	M38193.1
IL17	6p12	AL355513.11			U32659.1		
UCHL3	13q21.33	AL137244.28			NM_006002.1		
Other genes							
GGT1	22q11.23	D87002.1			L20490.1		
TGM1	14q11.2	M98447.1			M55183.1		

Table 2 Summary of genetic variations in 19 genes (*SNP* single-nucleotide polymorphism)

Gene	All genetic variations	SNPs	Insertion/ deletion polymorphisms	Novel	Total base pairs sequenced (kb)	Frequency (bp/1 SNP)
CYP						
CYP2A6	22	22	0	13	4.8	218
CYP2A13	15	15	0	11	6.7	447
CYP2B6	24	24	0	14	7.0	292
CYP2E	42	40	2	18	11.9	298
CYP2S1	19	14	5	9	6.5	464
TBXAS1	158	137	21	87	86.5	631
CYP7A1	18	16	2	13	9.0	563
CYP7B1	21	16	5	18	21.3	1331
Total (*CYP*)	319	284	35	183	153.7	(average) 541
Esterase						
AADAC	24	23	1	7	12.1	526
CEL	132	117	15	84	54.8	468
CES1	52	47	5	34	19.2	409
CES2	9	6	3	6	8.1	1350
ESD	29	28	1	14	22.3	796
GZMA	9	9	0	2	8.1	900
GZMB	14	13	1	10	6.4	492
IL17	11	11	0	6	7.8	709
UCHL3	60	48	12	47	32.8	683
Total (*Esterase*)	340	302	38	210	171.6	(average) 568
Others						
GGT1	7	7	0	7	2.6	371
TGM1	14	14	0	5	13.7	979
Total (*Others*)	21	21	0	12	16.3	(average) 776
Total (*All*)	680	607	73	405	341.6	563

(el-Zein et al. 1997; Oyama et al. 1997; Wu et al. 1997), nasopharyngeal carcinoma (Hildesheim et al. 1997), and oral cancer (Hung et al. 1997).

By screening a database of expressed-sequence tags, Rylander et al. (2001) have identified *CYP2S1*, a P450 enzyme that is expressed mainly in trachea, lung, stomach, small intestine, and spleen. Rivera et al. (2002) have reported that *CYP2S1* is inducible by 2,3,7,8-tetrachlorodibenzo-*p*-dioxin (dioxin) in a cell line derived from human lung epithelium.

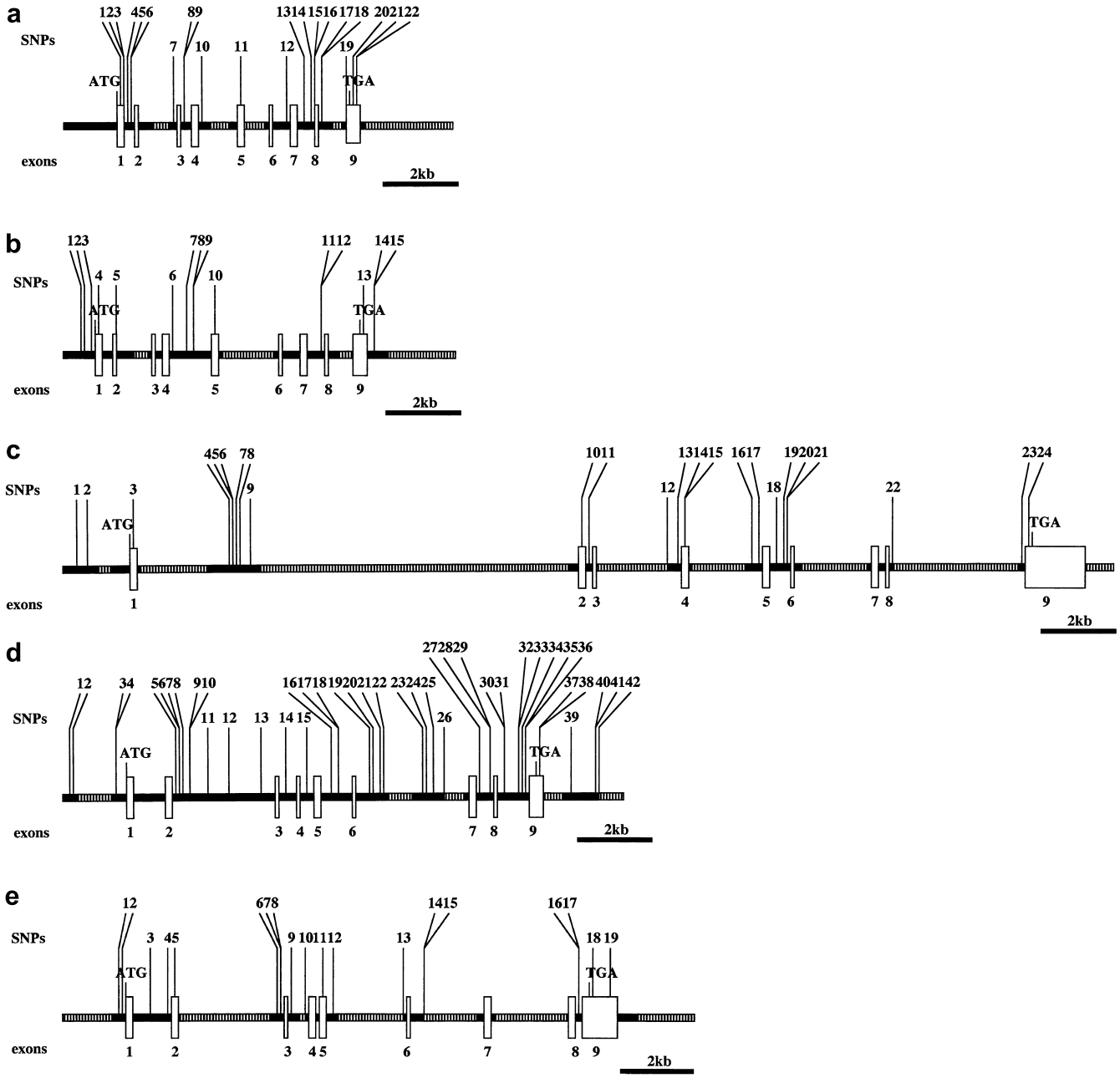

Fig. 1a–h Locations of single-nucleotide polymorphisms (SNPs) in the *CYP2A6* (**a**), *CYP2A13* (**b**), *CYP2B6* (**c**), *CYP2E* (**d**), *CYP2S1* (**e**), *TBXAS1* (**f**), *CYP7A1* (**g**), and *CYP7B1* (**h**) genes (*vertical lines*). *Open boxes* Exons, *hatching* unsequenced regions of repetitive elements, *ATG* initiation codon, *TGA, TAG* stop codons

Thromboxane A synthase (TBXAS1, CYP5A1) catalyzes the conversion of prostaglandin endoperoxide into thromboxane A2 (Shen and Tai 1986; Jones and Fitzpatrick 1991). TBXAS1 plays an important role in hemostasis and in cardiovascular diseases (FitzGerald et al. 1990). Although eleven polymorphisms have been identified in the promoter region, coding sequences, or 3'-untranslated region (3'UTR) of the *TBXAS1* gene, the biological effects of these variants are currently unknown (Chevalier et al. 2001).

CYP7A1 encodes cholesterol 7-alpha-hydroxylase, the rate-limiting enzyme for the conversion of cholesterol to bile acids in the liver (Jelinek et al. 1990). The promoter region of this gene contains a potential DNA-binding site for the transcription factor CPF; mutation of the CPF-binding site abolishes hepatic-specific expression in transient transfection assays (Nitta et al. 1999). Wang et al. (1998) have identified two linked polymorphisms in the 5'flanking region of *CYP7A1*; the allele defined by these polymorphisms is associated with increased concentrations of low-density lipoprotein cholesterol in plasma.

CYP7B1 encodes oxysterol 7-alpha-hydroxylase (Setchell et al. 1998). This enzyme not only participates the synthesis of primary bile acids from cholesterol but

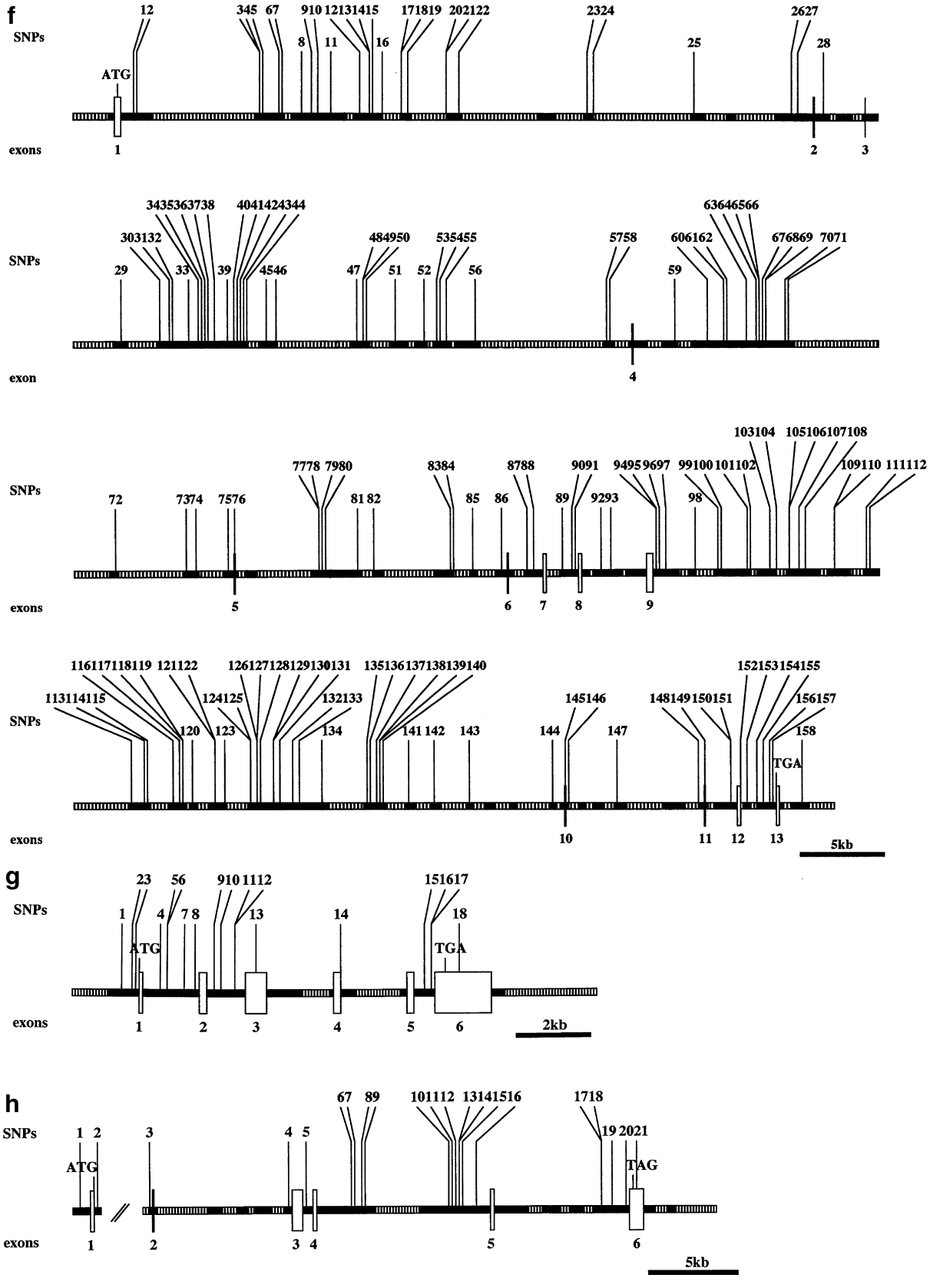

Fig. 1a–h (Continued)

Table 3 Summary of genetic variations detected in the *CYP2A6* gene, *CYP2A13* gene, *CYP2B6* gene, *CYP2E* gene, *CYP2S1* gene, *TBXAS1* gene, *CYP7A1* gene, and *CYP7B1* gene (*CYP2A6* Cytochrome P450, subfamily IIA, polypeptide 6, *CYP2A13* Cytochrome P450, subfamily IIA, polypeptide 13, *CYP2B6* Cytochrome P450, subfamily IIB, polypeptide 6, *CYP2E* Cytochrome P450, subfamily IIE, *CYP2S1* Cytochrome P450, subfamily IIS, polypeptide 1, *TBXAS1* Thromboxane A synthase 1, *CYP7A1* Cytochrome P450, subfamily VIIA, polypeptide 1, *CYP7B1* Cytochrome P450, subfamily VIIB, polypeptide 1, *NCBI* National Center for Biotechnology Information, *UTR* untranslated region, *del* deletion, *ins* insertion)

Gene and variation no.	Location	Position[a]	Genetic variation	NCBI SNP ID
CYP2A6				
1	Exon 1	31	C/T (Leu8Leu)	
2	Exon 1	60	G/A (Val17Val)	rs1137115
3	Exon 1	153	G/A (Gln48Gln)	
4	Intron 1	29	C/T	
5	Intron 1	98	G/A	
6	Intron 1	153	C/T	
7	Intron 2	1011	C/T	
8	Intron 3	23	G/T	
9	Intron 3	77	G/C	
10	Intron 4	275	A/G	rs2388868
11	Exon 5	117	C/T (Arg257Arg)	rs1809811
12	Intron 6	323	C/A	
13	Intron 7	203	G/A	
14	Intron 7	440	A/C	rs2316210
15	Exon 8	84	C/T (His415His)	rs2002977
16	Exon 8	96	G/C (Glu419Asp)	
17	Intron 8	27	C/T	rs2002976
18	Intron 8	47	G/C	rs2002975
19	Exon 9	109	T/C (Ile471Thr)[b]	
20	Exon 9	333	C/G (3'UTR)	rs696839
21	Exon 9	383	A/G (3'UTR)	
22	Exon 9	386	C/A (3'UTR)	
CYP2A13				
1	5' Flanking	−402	G/A	rs305987
2	5' Flanking	−251	C/T	
3	5' Flanking	−112	T/C	
4	Exon 1	83	G/A (Arg25Gln)	
5	Exon 2	121	C/T (Arg101Stop)	
6	Intron 4	118	T/C	
7	Intron 4	500	G/A	
8	Intron 4	673	C/G	
9	Intron 4	712	A/G	
10	Exon 5	115	C/T (Arg257Cys)[c]	
11	Intron 7	463	C/T	rs1709081
12	Intron 7	471	C/T	rs1645694
13	Exon 9	283	G/C (3'UTR)	
14	3' Flanking	145	T/G	
15	3' Flanking	157	G/A	
CYP2B6				
1	5' Flanking	−1449	T/C	rs2054675
2	5' Flanking	−1179	C/G	
3	Exon 1	71	C/T (Arg22Cys)[d]	
4	Intron 1	2608	G/A	rs2014141
5	Intron 1	2663	C/G	
6	Intron 1	2676	G/A	
7	Intron 1	2832	T/C	
8	Intron 1	2919	T/C	
9	Intron 1	3212	C/T	
10	Exon 2	45	G/C (Pro72Pro)[d]	rs2279341
11	Intron 2	111	C/T	
12	Intron 3	2124	G/T	
13	Intron 3	2441	C/T	
14	Exon 4	15	C/G (Pro167Ala)	rs3826711
15	Exon 4	32	G/T (Gln172His)[d]	rs3745274
16	Intron 4	1850	T/C	rs4061281
17	Intron 4	2048	G/A	
18	Intron 5	183	G/A	
19	Intron 5	402	C/T	rs2279345
20	Intron 5	488	A/G	
21	Intron 5	514	G/A	
22	Intron 8	53	C/T	
23	Intron 8	3731	A/G	rs2291287
24	Exon 9	165	C/T (Arg487Cys)[d]	rs3211371
CYP2E				
1	5' Flanking	−1621	G/C	rs3813865
2	5' Flanking	−1480	T/G	
3	5' Flanking	−317	A/G[e]	rs2070672

[a]For SNPs in the 5' flanking region, intron, or 3' flanking region, nucleotide positions are counted from the first intronic nucleotide at the exon/intron junction (for SNPs in the exon, nucleotide positions are counted from the first exonic nucleotide at the exon/intron junction)
[b]SNP previously reported by Ariyoshi et al. (2001)
[c]SNP previously reported by Zhang et al. (2002)
[d]SNP previously reported by Lang et al. (2001)
[e]SNPs previously reported by Fairbrother et al. (1998)
[f]SNP previously reported by Baek et al. (1996)
[g]SNP previously reported by Chevalier et al. (2001)

Table 3 (Continued)

Gene and variation no.	Location	Position[a]	Genetic variation	NCBI SNP ID
4	5' Flanking	−298	A/T[e]	rs2070673
5	Intron 2	15	C/T	
6	Intron 2	116	T/C	rs943975
7	Intron 2	171	C/G	rs1536828
8	Intron 2	344	C/A	
9	Intron 2	439	C/T	
10	Intron 2	500	G/A	
11	Intron 2	1023	T/G	
12	Intron 2	1594	T/C	rs915906
13	Intron 2	2567	T/C	
14	Intron 3	102	C/T	rs2070674
15	Intron 4	186	T/G	
16	Intron 5	324	C/T	rs2070675
17	Intron 5	555	C/A	rs915907
18	Intron 5	587	G/A	rs915908
19	Intron 6	326	A/G	
20	Intron 6	474	T/C	
21	Intron 6	625	G/A	
22	Intron 6	786	T/C	
23	Intron 6	1825	A/C	rs743534
24	Intron 6	1966	G/A	rs743535
25	Intron 6	2136	A/G	rs1410897
26	Intron 6	2400	C/T	rs1329149
27	Intron 7	117	T/G	
28	Intron 7	383	G/C	rs2070676
29	Intron 7	420	A/T	rs2070677
30	Intron 8	(217–219)	TGT/del	
31	Intron 8	(227–236)	$(T)_{9–11}$	
32	Intron 8	617	C/T	rs2515642
33	Intron 8	680	A/G	rs2480259
34	Intron 8	704	C/T	rs2480258
35	Intron 8	757	A/G	rs2249694
36	Intron 8	772	T/C	rs2249695
37	Exon 9	226	A/T (3'UTR)	rs2480257
38	Exon 9	231	A/G (3'UTR)	rs2480256
39	3' Flanking	879	G/T	rs1952467
40	3' Flanking	1501	C/T	
41	3' Flanking	1505	G/T	
42	3' Flanking	1631	G/T	
CYP2S1				
1	5' Flanking	−177	C/T	rs3810171
2	5' Flanking	−(22–24)	AGG/del	
3	Intron 1	540	G/C	
4	Intron 1	997	T/C	rs338600
5	Exon 2	45	C/G (Pro74Pro)	rs338599
6	Intron 2	2889	G/A	rs338595
7	Intron 2	(2991–3001)	$(A)_{10–11}$	
8	Intron 2	3046	T/C	rs338594
9	Intron 3	122	A/G	rs184623
10	Intron 3	471	T/C	rs338593
11	Exon 5	35	C/T (Leu230Leu)	
12	Intron 5	(245–248)	TCTC/del	
13	Intron 5	2301	A/G	rs1628289
14	Intron 6	(332–343)	$(A)_{11–12}$	
15	Intron 6	337	A/G	
16	Intron 8	109	C/G	rs338584
17	Intron 8	(157–172)	$(TC)_{7–8}$	
18	Exon 9	240	A/G (3'UTR)	rs338583
19	Exon 9	757	C/A (3'UTR)	
TBXAS1				
1	Intron 1	811	A/G	rs764746
2	Intron 1	(1060–1069)	$(T)_{10–13}$	
3	Intron 1	8545	C/T	
4	Intron 1	8592	G/A	
5	Intron 1	8815	C/G	
6	Intron 1	9827	A/G	
7	Intron 1	9940	T/C	rs2267679
8	Intron 1	−31741	C/T	rs2267680

Table 3 (Continued)

Gene and variation no.	Location	Position[a]	Genetic variation	NCBI SNP ID
9	Intron 1	−31099	G/C	rs2267681
10	Intron 1	−(30739–30752)	$(T)_{11–14}$	
11	Intron 1	−29832	C/T	
12	Intron 1	−28130	C/T	
13	Intron 1	−27482	C/G	
14	Intron 1	−27360	T/C	
15	Intron 1	−27182	G/T	
16	Intron 1	−26664	T/G	rs2267682
17	Intron 1	−25419	G/A	
18	Intron 1	−25391	G/A	
19	Intron 1	−25188	C/A	rs41708
20	Intron 1	−22669	G/C	
21	Intron 1	−22648	T/C	rs41707
22	Intron 1	−21974	C/T	
23	Intron 1	−13748	T/A	rs194150
24	Intron 1	−13512	T/C	rs194149
25	Intron 1	−7228	T/C	
26	Intron 1	−1368	C/T	
27	Intron 1	−883	A/T	rs3801154
28	Intron 2	508	T/C	
29	Intron 3	3741	C/T	
30	Intron 3	6106	A/del	
31	Intron 3	(6688–6689)	TG/del	
32	Intron 3	6894	A/G	
33	Intron 3	7924	G/A	
34	Intron 3	8393	A/G	rs2299887
35	Intron 3	8620	C/T	rs2299888
36	Intron 3	8825	C/T	rs2299889
37	Intron 3	9069	G/A	rs2299890
38	Intron 3	9360	T/C	
39	Intron 3	10282	G/C	rs2267684
40	Intron 3	(10750–10774)	$(T)_{22–25}$	
41	Intron 3	10822	G/C	rs1015572
42	Intron 3	11020	C/T	
43	Intron 3	11178	G/T	rs1015571
44	Intron 3	11371	G/T	rs1015570
45	Intron 3	12740	T/C	rs3801153
46	Intron 3	13193	T/C	
47	Intron 3	18241	T/A	
48	Intron 3	18569	G/A	
49	Intron 3	18656	A/G	rs2267688
50	Intron 3	18899	A/T	rs2267689
51	Intron 3	20654	G/A	
52	Intron 3	22444	A/G	rs2267696
53	Intron 3	(23376–23386)	$(T)_{10–12}$	
54	Intron 3	23471	C/T	
55	Intron 3	23793	G/A	
56	Intron 3	(25690–25704)	$(A)_{12–16}$	
57	Intron 3	33881	C/T	rs1978180
58	Intron 3	(34024–34026)	GAG/del	
59	Intron 4	2446	A/G	
60	Intron 4	4399	C/T	
61	Intron 4	(5554–5555)	C/ins	
62	Intron 4	5673	G/A	rs2267698
63	Intron 4	6881	A/T	rs2299891
64	Intron 4	7276	G/A	rs2299892
65	Intron 4	7453	C/T	
66	Intron 4	7470	A/G	rs2299893
67	Intron 4	(7645–7654)	$(T)_{9–10}$	
68	Intron 4	7756	C/T	
69	Intron 4	7770	T/C	
70	Intron 4	9099	G/A	rs2284204
71	Intron 4	9268	G/A	rs2284205
72	Intron 4	17600	T/C	rs3801152
73	Intron 4	22048	T/C	rs41734

Table 3 (Continued)

Gene and variation no.	Location	Position[a]	Genetic variation	NCBI SNP ID
74	Intron 4	(22506–22542)	TTGGTCCCCC-AACCGCCTG-TCTCCCCAC-ACCCCGCAA/del/AGGCTG CAGTCC/ins	
75	Intron 4	24582	C/A	
76	Exon 5	37	G/A (Val125Ile)	
77	Intron 5	(5127–5138)	$(T)_{9–12}$	
78	Intron 5	(5140–5141)	T/ins	
79	Intron 5	5483	G/A	rs2107901
80	Intron 5	5656	C/T	rs42335
81	Intron 5	7570	T/A	
82	Intron 5	8494	C/T	rs757760
83	Intron 5	13455	G/A	rs2190087
84	Intron 5	13591	T/C	rs757759
85	Intron 5	14656	G/A	rs1557968
86	Intron 5	16713	C/T	rs1557967
87	Intron 6	1001	T/C	
88	Intron 6	1455	G/A	rs917147
89	Intron 7	1203	C/T	
90	Intron 7	1815	T/C	rs3823717
91	Intron 7	1922	C/A	rs3735355
92	Intron 8	(1245–1274)	$(AC)_{12–15}$[f]	
93	Intron 8	2028	T/C	rs41727
94	Intron 9	40	T/C	rs2072179
95	Intron 9	139	G/C	
96	Intron 9	554	C/T	rs41726
97	Intron 9	872	G/A	rs41724
98	Intron 9	2643	A/C	rs41723
99	Intron 9	4164	C/T	rs41721
100	Intron 9	4299	C/T	rs41720
101	Intron 9	5862	T/C	
102	Intron 9	5978	C/T	
103	Intron 9	(7360–7369)	$(A)_{9–10}$	
104	Intron 9	(7562–7563)	A/ins	
105	Intron 9	8385	C/T	rs41717
106	Intron 9	8462	T/G	rs42334
107	Intron 9	9085	A/T	
108	Intron 9	9441	G/T	
109	Intron 9	11304	T/G	rs41716
110	Intron 9	(11323–11338)	$(T)_{13–16}$	
111	Intron 9	13259	C/del	
112	Intron 9	13478	T/C	rs740150
113	Intron 9	(17698–17707)	$(T)_{9–10}$	
114	Intron 9	18399	A/G	rs193950
115	Intron 9	(18709–18719)	$(A)_{10–12}$	
116	Intron 9	20380	G/T	
117	Intron 9	20607	G/A	
118	Intron 9	20611	T/C	rs193947
119	Intron 9	20649	T/C	rs193946
120	Intron 9	(21300–21308)	$(T)_{8–9}$	
121	Intron 9	22829	C/A	
122	Intron 9	22919	T/C	
123	Intron 9	23463	T/C	rs3801150
124	Intron 9	25019	C/T	rs2108033
125	Intron 9	25072	T/G	
126	Intron 9	25551	A/G	rs2267703
127	Intron 9	25641	G/A	
128	Intron 9	25763	G/T	
129	Intron 9	26532	T/C	
130	Intron 9	26542	C/T	
131	Intron 9	26792	C/G	
132	Intron 9	28687	A/T	
133	Intron 9	28989	G/A	
134	Intron 9	29606	C/A	
135	Intron 9	32268	T/C	rs3801148
136	Intron 9	32429	C/T	

Table 3 (Continued)

Gene and variation no.	Location	Position[a]	Genetic variation	NCBI SNP ID
137	Intron 9	32912	A/G	
138	Intron 9	33084	G/A	rs2284212
139	Intron 9	33183	C/A	
140	Intron 9	33362	A/G	rs2284213
141	Intron 9	34811	C/T	
142	Intron 9	36495	G/A	
143	Intron 9	38683	C/G	
144	Intron 9	43855	T/C	
145	Exon 10	25	G/A (Glu388Lys)	rs3735354
146	Intron 10	158	G/A	rs740204
147	Intron 10	3166	T/C	rs3823715
148	Intron 10	8360	A/G	rs2286200
149	Exon 11	119	G/A (Glu450Lys)[g]	
150	Intron 11	1518	C/T	rs757835
151	Intron 11	1540	T/C	rs757834
152	Exon 12	138	G/A (Arg502Gln)	
153	Intron 12	514	C/G	rs2240395
154	Intron 12	1073	T/G	
155	Intron 12	1551	G/A	rs2072190
156	Intron 12	1806	C/G	
157	Intron 12	2033	G/A	
158	3' Flanking	1402	C/T	
CYP7A1				
1	5' Flanking	−469	C/T	rs3824260
2	5' Flanking	−203	C/A	rs3808607
3	5' Flanking	−(114–105)	$(T)_{9–10}$	
4	Intron 1	512	C/A	
5	Intron 1	607	C/T	
6	Intron 1	611	T/C	
7	Intron 1	1184	G/A	
8	Intron 1	1536	C/T	rs2162459
9	Intron 2	156	G/A	rs1457042
10	Intron 2	349	G/A	rs1457043
11	Intron 2	770	A/G	
12	Intron 2	782	T/C	
13	Exon 3	377	A/G (Asn233Ser)	
14	Exon 4	131	G/A (Asp347Asn)	
15	Intron 5	(249–257)	$(T)_{8–9}$	
16	Intron 5	471	T/C	
17	Intron 5	566	A/G	
18	Exon 6	758	G/A (3'UTR)	
CYP7B1				
1	5'Flanking	−595	A/G	
2	Intron 1	19	A/T	
3	Intron 1	−(19–9)	$(T)_{9–12}$	
4	Intron 2	(8107–8117)	$(T)_{10–11}$	
5	Intron 3	(158–171)	$(T)_{12–14}$	
6	Intron 4	2144	G/A	
7	Intron 4	2280	A/C	
8	Intron 4	2626	T/C	
9	Intron 4	2841	G/T	
10	Intron 4	(7610–7627)	$(A)_{16–19}$	
11	Intron 4	(7846–7851)	$(A)_{6–7}$	
12	Intron 4	8004	G/T	
13	Intron 4	8217	A/G	rs3779872
14	Intron 4	8267	G/C	
15	Intron 4	8417	T/C	rs3779870
16	Intron 4	9226	G/C	rs3779869
17	Intron 5	6213	G/T	
18	Intron 5	6224	A/G	
19	Intron 5	6629	G/C	
20	Intron 5	7545	T/C	
21	Exon 6	337	C/T (3'UTR)	

Table 4 Number and regions of SNPs detected in 19 genes (*SNP* single-nucleotide polymorphism, *UTR* untranslated region)

Gene	5' Flanking	Intron	3' Flanking	Exon				Total
				5'UTR	Coding		3'UTR	
					Nonsynonymous	Synonymous		
CYP								
CYP2A6	0	12	0	0	2	5	3	22
CYP2A13	3	6	2	0	3	0	1	15
CYP2B6	2	17	0	0	4	1	0	24
CYP2E	4	30	4	0	0	0	2	40
CYP2S1	1	9	0	0	0	2	2	14
TBXAS1	0	132	1	0	4	0	0	137
CYP7A1	2	11	0	0	2	0	1	16
CYP7B1	1	14	0	0	0	0	1	16
Total (*CYP*)	13	231	7	0	15	8	10	284
Esterase								
AADAC	0	20	0	1	1	0	1	23
CEL	1	111	0	0	0	4	1	117
CES1	3	40	4	0	0	0	0	47
CES2	0	3	1	0	1	0	1	6
ESD	1	25	1	0	1	0	0	28
GZMA	3	5	0	0	0	1	0	9
GZMB	4	2	4	0	2	0	1	13
IL17	4	4	1	0	0	0	2	11
UCHL3	5	42	1	0	0	0	0	48
Total (*Esterase*)	21	252	12	1	5	5	6	302
Others								
GGT1	3	2	0	0	1	1	0	7
TGM1	0	11	0	0	0	1	2	14
Total (*Others*)	3	13	0	0	1	2	2	21
Total (*All*)	37	496	19	1	21	15	18	607

Table 5 Novel SNPs detected in exons of 19 genes (*SNP* single-nucleotide polymorphism, *UTR* untranslated region)

Region		Gene	Location	Position	SNP
Coding	Nonsynonymous	*CYP2A6*	Exon8	96	G/C (Glu419Asp)
		CYP2A13	Exon1	83	G/A (Arg25Gln)
			Exon2	121	C/T (Arg101Stop)
		TBXAS1	Exon5	37	G/A(Val125Ile)
			Exon12	138	G/A (Arg502Gln)
		CYP7A1	Exon3	377	A/G (Asn233Ser)
			Exon4	131	G/A (Asp347Asn)
		CES2	Exon5	60	G/A (Arg206His)
		GZMB	Exon2	109	A/G (Gln55Arg)
		GGT1	Exon1	49	C/G (His17Asp)
	Synonymous	*CYP2A6*	Exon1	31	C/T (Leu8Leu)
			Exon1	153	G/A (Gln48Gln)
		CYP2S1	Exon5	35	C/T (Leu230Leu)
		CEL	Exon9	137	C/T (Phe347Phe)
			Exon10	82	C/T (Thr391Thr)
			Exon12	583	C/A (Ala692Ala)
		GGT1	Exon3	68	G/T (Val124Val)
		TGM1	Exon2	179	C/T (Asp59Asp)
3'UTR		*CYP2A6*	Exon9	383	A/G
			Exon9	386	C/A
		CYP2A13	Exon9	283	G/C
		CYP2S1	Exon9	757	C/A
		CYP7A1	Exon6	758	G/A
		CYP7B1	Exon6	337	C/T
		CEL	Exon12	759	T/C
		CES2	Exon12	256	A/G
		TGM1	Exon15	369	C/A

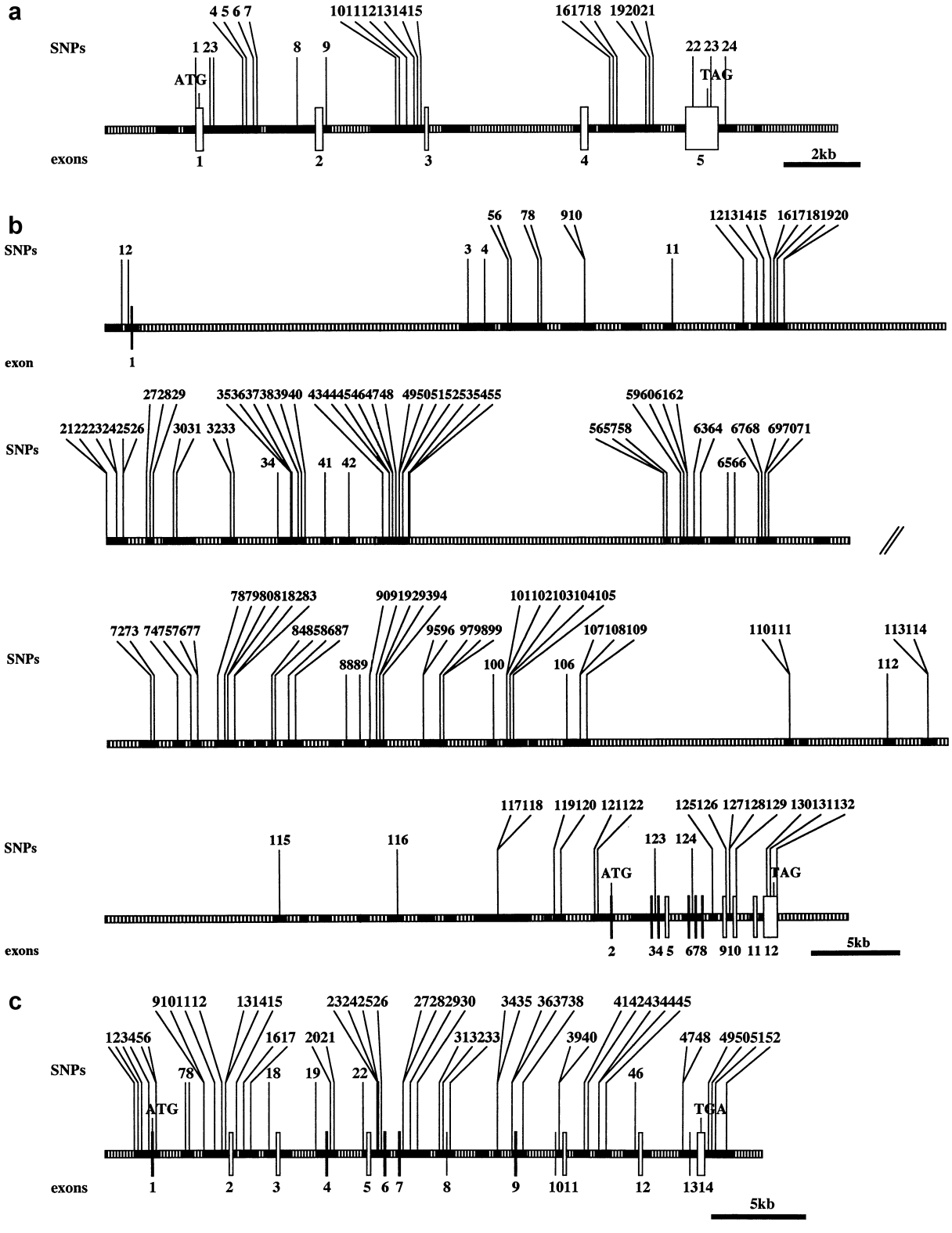

Fig. 2a–i Locations of single-nucleotide polymorphisms (SNPs) in the *AADAC* (**a**), *CEL* (**b**), *CES1* (**c**), *CES2* (**d**), *ESD* (**e**), *GZMA* (**f**), *GZMB* (**g**), *IL17* (**h**), and *UCHL3* (**i**) genes (*vertical lines*). *Open boxes* Exons, *hatching* regions of repetitive elements, *ATG* initiation codon, *TGA, TAG, TAA* stop codons

also may be involved in neurosteroid metabolism, synthesis of sex hormones, and detoxification of oxysterols (Setchell et al. 1998; Wu et al. 1999). Mutation in the *CYP7B1* gene causes severe neonatal liver disease,

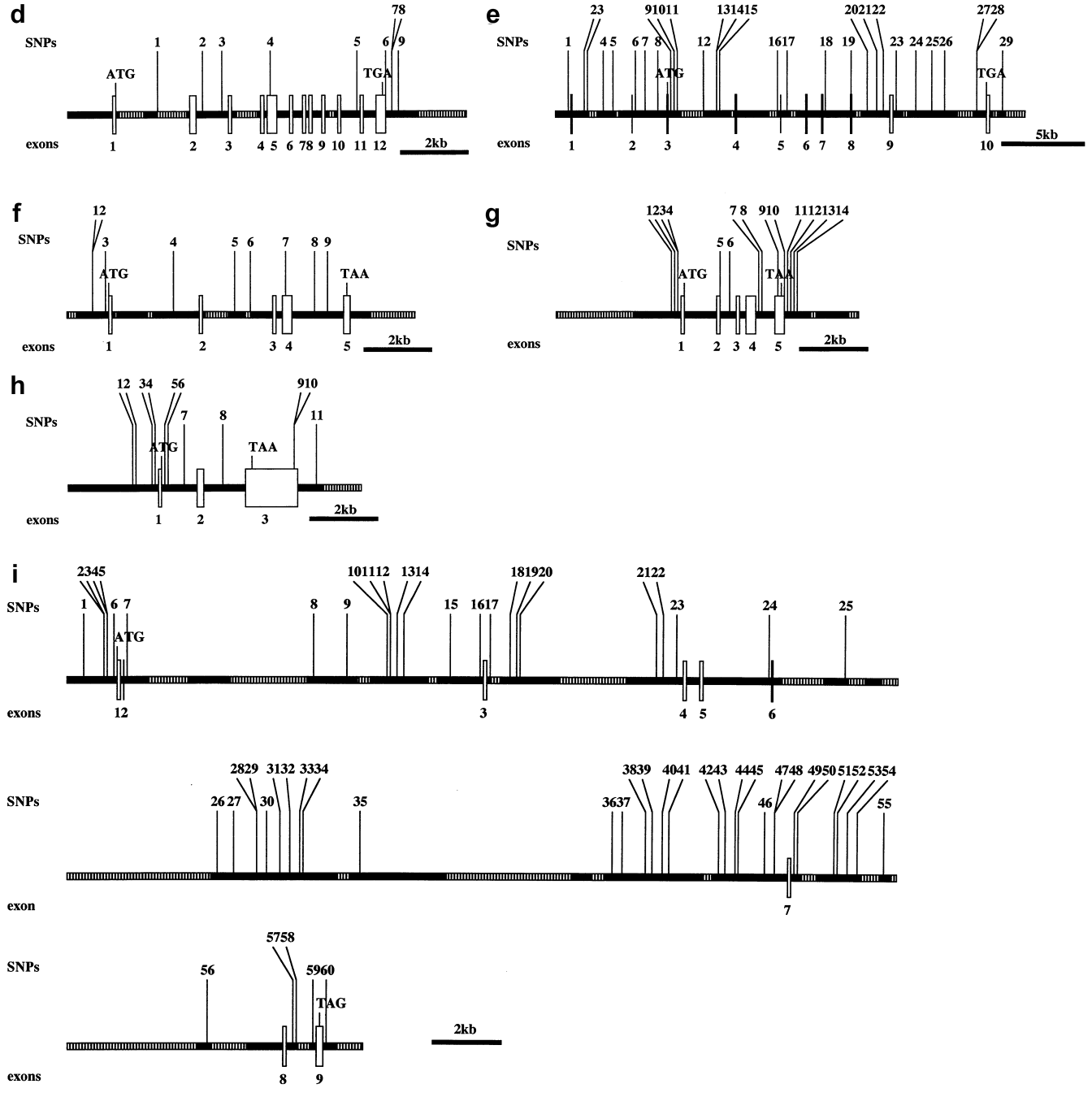

Fig. 2a–i (Continued)

an inborn error of bile acid synthesis (Setchell et al. 1998).

Arylacetamide deacetylase (AADAC) is an esterase involved in the metabolic activation of arylamine substrates that ultimately become carcinogenic (Probst et al. 1991). The *AADAC* gene is expressed in liver, adrenal cortex, adrenal medulla, and pancreas (Trickett et al. 2001).

Carboxyl-ester lipase (CEL), also called cholesterol esterase, plays an important role in the hydrolysis and absorption of cholesterol and lipid-soluble vitamin esters (Lombardo et al. 1980). The 3' portion of the *CEL* gene is characterized by a GC-rich region (Nilsson et al. 1990), and by a variable number of tandem-repeats sequence (Higuchi et al. 2002).

Carboxylesterases (CESs) constitute a group of serine-dependent esterases (Munger et al. 1991). These enzymes catalyze the hydrolysis of many different endogenous and xenobiotic compounds and play roles in the metabolism of numerous drugs that contain ester and amide bonds (Satoh and Hosokawa 1998). CES1 and CES2, two human-liver carboxylesterases selected for this study, differ in their substrate specificity (Dean et al. 1991; Brzezinski et al. 1994).

Table 6 Summary of genetic variations detected in the *AADAC* gene, *CEL* gene, *CES1* gene, *CES2* gene, *ESD* gene, *GZMA* gene, *GZMB* gene, *IL17* gene, *UCHL3* gene (*AADAC* arylacetamide deacetylase, *CEL* carboxyl-ester lipase, *CES1* carboxylesterase 1, *CES2* carboxylesterase 2, *ESD* esterase D, *GZMA* granzyme A, *GZMB* granzyme B, *IL17* interleukin 17, *UCHL3* ubiquitin carboxyl-terminal esterase L3, *NCBI* National Center for Biotechnology Information)

Gene and variation no.	Location	Position[a]	Genetic variation	NCBI SNP ID
1	Exon 1	29	C/T (5'UTR)	rs2293004
2	Intron 1	138	G/A	rs2293003
3	Intron 1	142	C/T	rs2293002
4	Intron 1	1033	A/G	
5	Intron 1	1253	T/C	rs1520137
6	Intron 1	1366	A/G	
7	Intron 1	1369	A/C	rs1520136
8	Intron 1	2501	C/A	rs2166264
9	Intron 2	46	A/G	rs2271942
10	Intron 2	1971	A/C	rs3772441
11	Intron 2	1988	A/G	rs3772440
12	Intron 2	2341	C/T	
13	Intron 2	2546	T/A	rs2271941
14	Intron 2	2609	T/C	
15	Intron 2	2663	T/C	rs2271940
16	Intron 4	605	T/C	
17	Intron 4	621	G/T	rs1546687
18	Intron 4	679	A/G	rs1546686
19	Intron 4	1680	C/T	rs2410838
20	Intron 4	1748	T/C	
21	Intron 4	1771	G/A	rs930589
22	Exon 5	238	A/G (Ile281Val)	rs1803155
23	Exon 5	678	A/G (3'UTR)	rs1042201
24	3' Flanking	208	A/del	
CEL				
1	5' Flanking	−(611–617)	$(A)_{6–7}$	
2	5' Flanking	−72	C/A	rs1324194
3	Intron 1	20098	T/G	
4	Intron 1	(20911–20924)	$(A)_{13–15}$	
5	Intron 1	22374	A/G	
6	Intron 1	(22460–22469)	$(T)_{9–10}$	
7	Intron 1	24205	T/G	
8	Intron 1	(24404–24417)	$(A)_{11–14}$	
9	Intron 1	26983	T/G	
10	Intron 1	(26983–26999)	$(T)_{14–17}$	
11	Intron 1	(32166–32174)	$(A)_{8–9}$	
12	Intron 1	36410	G/C	rs721577
13	Intron 1	37217	T/G	
14	Intron 1	37685	T/A	
15	Intron 1	38032	T/C	
16	Intron 1	38133	A/C	
17	Intron 1	38169	A/T	
18	Intron 1	38333	A/G	rs942389
19	Intron 1	38544	T/C	
20	Intron 1	(38642–38643)	G/ins	
21	Intron 1	48384	A/G	rs642806
22	Intron 1	48429	A/C	
23	Intron 1	49038	A/G	
24	Intron 1	49040	T/G	
25	Intron 1	49256	C/A	
26	Intron 1	49386	C/A	
27	Intron 1	50786	G/A	
28	Intron 1	50977	T/C	
29	Intron 1	51150	C/G	
30	Intron 1	52333	A/C	
31	Intron 1	52589	C/A	
32	Intron 1	55838	G/A	
33	Intron 1	56028	G/C	
34	Intron 1	58738	G/A	
35	Intron 1	59358	A/G	
36	Intron 1	59359	C/T	
37	Intron 1	59464	C/G	
38	Intron 1	59827	C/T	rs1408314
39	Intron 1	59917	A/G	rs613444
40	Intron 1	60071	G/A	rs522594
41	Intron 1	61340	C/G	
42	Intron 1	62739	A/G	
43	Intron 1	(64764–64779)	$(T)_{14–17}$	

[a]For SNPs in the 5' flanking region, intron, or 3' flanking region, nucleotide positions are counted from the first intronic nucleotide at the exon/intron junction (for SNPs in the exon, nucleotide positions are counted from the first exonic nucleotide at the exon/intron junction)

Table 6 (Continued)

Gene and variation no.	Location	Position[a]	Genetic variation	NCBI SNP ID
44	Intron 1	65243	T/C	
45	Intron 1	65269	T/A	
46	Intron 1	65325	G/C	
47	Intron 1	(65326–65334)	$(G)_{7–9}$	
48	Intron 1	65524	A/C	
49	Intron 1	65753	A/G	rs616906
50	Intron 1	65869	A/T	
51	Intron 1	65910	G/C	
52	Intron 1	66000	C/A	
53	Intron 1	66153	G/T	rs518054
54	Intron 1	66179	G/A	rs518139
55	Intron 1	(66226–66235)	$(A)_{9–10}$	
56	Intron 1	81620	C/T	rs1998584
57	Intron 1	81632	G/A	rs1998585
58	Intorn 1	81816	A/G	
59	Intron 1	82665	T/G	rs1324171
60	Intron 1	82760	C/A	rs626778
61	Intron 1	82963	T/C	rs992457
62	Intron 1	83054	T/C	rs625476
63	Intron 1	83480	T/C	
64	Intron 1	83732	T/C	
65	Intron 1	85507	A/T	
66	Intron 1	85688	C/T	rs524126
67	Intron 1	87299	G/A	
68	Intron 1	87426	G/C	
69	Intron 1	87587	A/G	rs789585
70	Intron 1	87670	T/C	
71	Intron 1	87738	A/G	rs789586
72	Intron 1	−(77494–77503)	$(A)_{9–10}$	
73	Intron 1	−77368	G/C	
74	Intron 1	−76075	A/C	rs2773818
75	Intron 1	−(75129–75135)	$(G)_{6–7}$	
76	Intron 1	−74785	G/C	
77	Intron 1	−74755	A/G	rs2905069
78	Intron 1	−73596	T/G	rs2073577
79	Intron 1	−73099	C/T	
80	Intron 1	−73002	A/C	rs2073578
81	Intron 1	−72962	C/T	rs633153
82	Intron 1	−72610	C/G	rs2073579
83	Intron 1	−72559	G/A	
84	Intron 1	−70235	G/A	rs681470
85	Intron 1	−70098	T/C	
86	Intron 1	−69440	C/T	
87	Intron 1	−68896	G/A	rs667805
88	Intron 1	−65848	A/G	rs601163
89	Intron 1	−65270	G/del	
90	Intron 1	−64434	C/T	rs3011266
91	Intron 1	−64070	C/T	rs629406
92	Intron 1	−63966	C/T	
93	Intron 1	−63916	C/T	
94	Intron 1	−63737	G/C	rs873202
95	Intron 1	−61309	G/C	rs944204
96	Intron 1	−61291	A/C	rs944205
97	Intron 1	−60392	C/T	
98	Intron 1	−60321	A/T	
99	Intron 1	−60318	C/T	
100	Intron 1	−56852	C/A	
101	Intron 1	−56375	A/G	rs1755629
102	Intron 1	−56312	G/C	rs1633769
103	Intron 1	−56133	C/T	
104	Intron 1	−56047	C/T	rs524137
105	Intron 1	−55964	G/A	
106	Intron 1	−52801	A/T	rs682437
107	Intron 1	−52016	G/A	
108	Intron 1	−51998	G/A	
109	Intron 1	−51578	G/C	rs3011272
110	Intron 1	−39557	T/C	

Table 6 (Continued)

Gene and variation no.	Location	Position[a]	Genetic variation	NCBI SNP ID
111	Intron 1	−39490	A/C	rs2905088
112	Intron 1	−33753	G/A	rs621808
113	Intron 1	−(31332–31340)	$(A)_{8–9}$	
114	Intron 1	−31321	C/T	rs650627
115	Intron 1	−19634	C/T	
116	Intron 1	−12651	G/A	rs2283130
117	Intron 1	−6643	T/C	rs645841
118	Intron 1	−6589	T/C	
119	Intron 1	−(3340–3345)	$(C)_{4–6}$	
120	Intron 1	−2946	G/A	rs586977
121	Intron 1	−839	A/C	rs658107
122	Intron 1	−699	A/G	rs668809
123	Intron 3	35	G/A	
124	Intron 6	157	C/T	
125	Intron 8	917	A/G	rs2013751
126	Exon 9	137	C/T (Phe347Phe)	
127	Intron 9	41	A/G	
128	Intron 9	151	T/C	
129	Exon 10	82	C/T (Thr391Thr)	
130	Exon 12	226	C/T (Pro573Pro)	rs488087
131	Exon 12	583	C/A (Ala692Ala)	
132	Exon 12	759	T/C (3'UTR)	
CES1				
1	5' Flanking	−983	T/C	
2	5' Flanking	−814	A/C	rs3785161
3	5' Flanking	−672	C/T	rs1974708
4	5' Flanking	−248	G/del	
5	Intron 1	22	T/del	
6	Intron 1	30	G/T	
7	Intron 1	1662	C/A	
8	Intron 1	1726	A/C	
9	Intron 1	2716	T/G	
10	Intron 1	(2747–2749)	AAA/del	
11	Intron 1	3288	A/del	
12	Intron 1	3691	T/G	
13	Intron 1	3819	A/G	
14	Intron 1	3880	G/A	rs3826184
15	Intron 2	74	T/C	rs3848300
16	Intron 2	552	C/A	
17	Intron 2	885	T/C	
18	Intron 2	2001	G/A	
19	Intron 3	2119	T/C	rs3815586
20	Intron 4	127	G/A	
21	Intron 4	347	T/G	
22	Intron 4	(1984–1985)	C/ins	
23	Intron 5	766	T/C	
24	Intron 5	825	T/G	rs2307235
25	Intron 5	828	C/T	rs2307233
26	Intron 5	868	T/A	rs2307229
27	Intron 7	68	C/G	
28	Intron 7	129	A/C	rs1833250
29	Intron 7	681	A/G	
30	Intron 7	885	T/C	
31	Intron 7	2151	C/G	
32	Intron 7	2470	G/A	
33	Intron 8	128	A/C	rs2302719
34	Intron 8	2618	T/C	
35	Intron 8	2665	G/A	
36	Intron 8	3785	G/A	rs3859093
37	Intron 8	3791	T/C	rs3859092
38	Intron 9	126	A/G	rs1965658
39	Intron 10	222	C/T	rs2244614
40	Intron 10	230	A/C	rs2244613

Table 6 (Continued)

Gene and variation no.	Location	Position[a]	Genetic variation	NCBI SNP ID
41	Intron 11	1177	C/G	
42	Intorn 11	1311	A/G	
43	Intron 11	2025	A/G	rs2168610
44	Intorn 11	2029	A/C	
45	Intorn 11	2317	T/C	
46	Intron 11	3887	C/T	
47	Intron 12	2311	G/A	
48	Intron 12	2331	C/G	rs3815589
49	3' Flanking	71	T/C	rs2287194
50	3' Flanking	362	G/A	
51	3' Flanking	581	C/T	
52	3' Flanking	1348	G/C	
CES2				
1	Intron 1	(1303–1321)	$(A)_{17–19}$	
2	Intron 2	229	C/A	rs2241410
3	Intorn2	824	T/C	rs2303218
4	Exon 5	60	G/A (Arg206His)	
5	Intorn10	406	G/A	rs2241409
6	Exon 12	256	A/G (3'UTR)	
7	3' Flanking	(155–172)	$(A)_{16–18}$	
8	3' Flanking	(173–178)	$(GA)_{3–6}$	
9	3' Flanking	377	C/G	
ESD				
1	5' Flanking	−333	G/A	rs1216969
2	Intron 1	603	C/T	rs1216967
3	Intron 1	698	C/T	rs1216966
4	Intron 1	1864	G/C	
5	Intron 1	2389	G/A	
6	Intron 2	22	T/C	
7	Intron 2	589	G/A	rs1216964
8	Intron 2	1499	C/T	rs1923880
9	Intron 3	92	C/A	
10	Intron 3	422	C/T	
11	Intron 3	581	C/T	
12	Intron 3	2270	G/A	
13	Intron 3	2951	A/G	rs1216961
14	Intron 3	3003	G/A	
15	Intron 3	3097	G/C	
16	Intron 4	2616	A/G	
17	Intron 5	392	C/T	rs1923890
18	Intron 7	107	T/C	rs2275680
19	Exon 8	68	A/G (Glu190Gly)	rs9778
20	Intron 8	1091	G/T	rs1216955
21	Intron 8	1652	A/G	
22	Intron 8	2048	G/C	rs1216956
23	Intron 9	188	G/A	rs2298087
24	Intron 9	(1523–1526)	$(TC)_{2–3}$	
25	Intron 9	2468	A/G	rs1341748
26	Intron 9	3362	A/G	
27	Intron 9	5292	T/C	rs1216959
28	Intron 9	5298	A/C	rs1216958
29	3' Flanking	798	A/G	
GZMA				
1	5' Flanking	−424	A/G	rs2069187
2	5' Flanking	−408	T/C	rs2069186
3	5' Flanking	−134	G/C	rs3136555
4	Intron 1	1947	A/T	rs3136556
5	Intron 2	958	C/T	rs3091252
6	Intron 2	1525	G/A	
7	Exon 4	105	C/G (Gly154Gly)	rs1051846
8	Intron 4	696	A/G	rs3091251
9	Intron 4	1141	G/A	

Table 6 (Continued)

Gene and variation no.	Location	Position[a]	Genetic variation	NCBI SNP ID
GZMB				
1	5' Flanking	−961	T/C	
2	5' Flanking	−263	A/G	
3	5' Flanking	−15	C/T	rs2273844
4	5' Flanking	−10	A/G	rs2273843
5	Exon 2	109	A/G (Gln55Arg)	
6	Intron 2	(242–243)	A/ins	
7	Intron 4	131	G/A	
8	Intron 4	182	G/A	
9	Exon 5	139	T/C (Tyr247His)	rs2236338
10	Exon 5	174	A/G (3'UTR)	rs2236337
11	3' Flanking	54	C/T	
12	3' Flanking	184	G/T	
13	3' Flanking	256	T/A	
14	3' Flanking	406	G/A	
IL17				
1	5' Flanking	−832	A/G	
2	5' Flanking	−692	C/T	
3	5' Flanking	−152	A/G	rs2275913
4	5' Flanking	−76	G/A	
5	Intron 1	18	G/A	rs3819025
6	Intron 1	126	A/G	
7	Intron 1	762	G/A	
8	Intron 2	594	A/T	rs3804513
9	Exon 3	1483	C/T (3'UTR)	rs1974226
10	Exon 3	1487	C/T (3'UTR)	rs3748067
11	3' Flanking	657	G/T	
UCHL3				
1	5' Flanking	−1034	A/G	
2	5' Flanking	−490	G/C	rs3812845
3	5' Flanking	−480	T/C	rs3812844
4	5' Flanking	−295	T/C	
5	5' Flanking	−258	A/G	rs2281762
6	5' Flanking	−(25–11)	GGCGAAGG-CGGCGGC/del	
7	Intron 2	28	T/C	
8	Intron 2	(5639–5640)	ATA/ins	
9	Intron 2	6638	C/T	rs1323696
10	Intron 2	7862	G/A	
11	Intron 2	(7936–7947)	$(T)_{11–12}$	
12	Intron 2	(7975–7988)	$(T)_{12–14}$	
13	Intron 2	8117	A/C	
14	Intron 2	8361	G/A	
15	Intron 2	9800	C/T	
16	Intron 2	(10738–10747)	$(T)_{9–10}$	
17	Intron 3	11	A/T	
18	Intron 3	(662–675)	$(TA)_{6–7}$	
19	Intron 3	866	T/C	
20	Intron 3	(944–945)	TGTATACGTAT-ACATACGTA-TACATATAT-ACATACGTA-TATA/ins	
21	Intron 3	5052	T/C	
22	Intron 3	5282	T/C	
23	Intron 3	5617	G/A	rs2031235
24	Intron 5	2124	T/C	rs2296146
25	Intron 6	2191	C/T	
26	Intron 6	8264	G/C	
27	Intron 6	(8741–8744)	ATTT/del	
28	Intron 6	9411	T/G	
29	Intron 6	9459	T/A	
30	Intron 6	9772	T/C	

Table 6 (Continued)

Gene and variation no.	Location	Position[a]	Genetic variation	NCBI SNP ID
31	Intron 6	10158	C/T	
32	Intron 6	10412	C/G	rs966058
33	Intron 6	10707	T/C	rs966059
34	Intron 6	10839	A/C	
35	Intorn 6	12493	A/G	
36	Intron 6	20153	G/A	rs974373
37	Intron 6	(20435–20437)	CCT/del	
38	Intron 6	21202	C/T	
39	Intron 6	21295	T/C	
40	Intron 6	21639	C/T	rs3783028
41	Intron 6	21778	A/G	
42	Intron 6	23299	T/C	
43	Intron 6	23498	A/G	
44	Intron 6	23790	A/T	
45	Intron 6	23894	A/C	
46	Intron 6	(24729–24732)	TGTT/del	
47	Intron 6	(25083–25084)	A/ins	
48	Intron 6	25084	C/T	
49	Intron 7	93	T/G	rs2274046
50	Intron 7	221	C/G	rs2274047
51	Intron 7	1342	G/A	
52	Intron 7	1387	G/A	
53	Intron 7	1760	T/G	
54	Intron 7	2096	G/A	
55	Intron 7	2873	T/G	
56	Intron 7	7554	T/A	
57	Intron 8	207	T/A	
58	Intron 8	252	C/G	
59	Intron 8	(883–892)	$(T)_{9–10}$	
60	3' Flanking	7	T/G	rs2274048

Esterase D (ESD), a member of a group of nonspecific esterases, is especially abundant in liver and kidney (Lee et al. 1986). The gene encoding human ESD is a useful genetic marker for retinoblastoma (Lee and Lee 1986).

Granzymes are cytotoxic T-lymphocyte-associated serine esterases (Masson and Tschopp 1987). Granzymes A (*GZMA*) and B (*GZMB*) are the most abundantly expressed of the granzymes (Henkart 1994). Both are involved in apoptotic processes, but each uses a distinct pathway (Beresford et al. 1999; Shresta et al. 1999). The GZMA pathway slowly induces apoptosis of target cells, whereas GZMB appears to facilitate the induction of apoptosis (Shi et al. 1992a, 1992b).

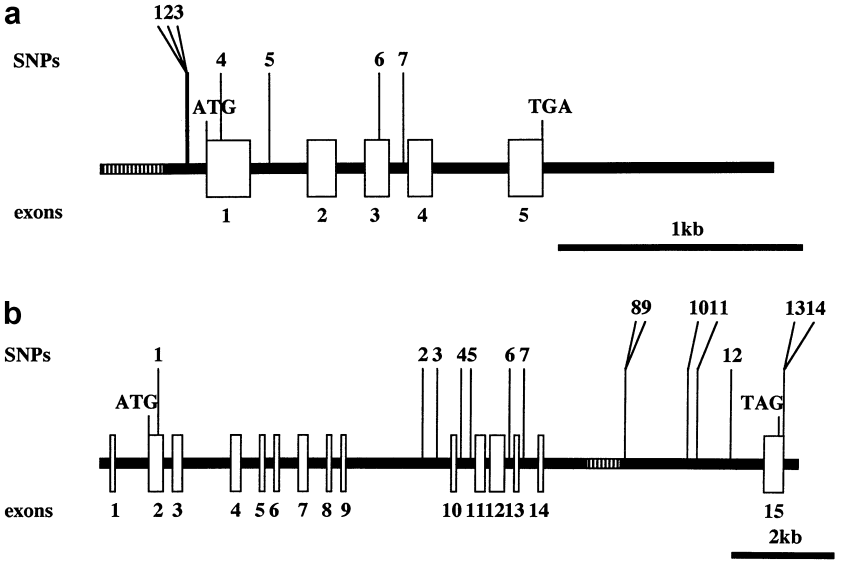

Fig. 3a, b Locations of single-nucleotide polymorphisms (SNPs) in the *GGT1* (**a**) and *TGM1* (**b**) genes (*vertical lines*). *Open boxes* Exons, *hatching* regions of repetitive elements, *ATG* initiation codon, *TGA, TAG* stop codons

Table 7 Summary of genetic variations detected in the *GGT1* gene and *TGM1* gene (*GGT1* gamma-glutamyltransferase 1, *TGM1* Transglutaminase 1, *NCBI* National Center for Biotechnology Information)

Gene and variation no.	Location	Position[a]	Genetic variation	NCBI SNP ID
GGT1				
1	5' Flanking	−105	C/T	
2	5' Flanking	−96	T/C	
3	5' Flanking	−87	A/G	
4	Exon 1	49	C/G (His17Asp)	
5	Intron 1	85	G/A	
6	Exon 3	68	G/T (Val124Val)	
7	Intron 3	−25	T/C	
TGM1				
1	Exon 2	179	C/T (Asp59Asp)	
2	Intron 9	1594	C/T	rs2748525
3	Intron 9	1933	C/G	rs3783442
4	Intron 10	54	C/T	rs3742506
5	Intron 10	420	A/G	rs2273303
6	Intron 12	101	T/G	
7	Intron 13	72	G/A	
8	Intron 14	1671	C/G	rs2277486
9	Intron 14	1691	G/A	rs2256989
10	Intron 14	2983	G/A	rs2855094
11	Intron 14	3158	T/C	
12	Intron 14	3816	G/C	rs2855098
13	Exon 15	233	T/C (3'UTR)	rs2229463
14	Exon 15	369	C/A (3'UTR)	

[a]For SNPs in the 5' flanking region, intron, or 3' flanking region, nucleotide positions are counted from the first intronic nucleotide at the exon/intron junction (for SNPs in the exon, nucleotide positions are counted from the first exonic nucleotide at the exon/intron junction)

Interleukin 17 (IL17), also known as cytotoxic T-lymphocyte-associated serine esterase, is secreted by activated memory $CD4^+$ T cells and modulates the early stage of the immune response (Rouvier et al. 1993; Broxmeyer 1996). High levels of IL-17 may be associated with several chronic inflammatory diseases (Kotake et al. 1999; Molet et al. 2001; Laan et al. 2002).

Ubiquitin carboxyl-terminal esterase L3 (UCHL3) catalyzes C-terminal esters and amides of ubiquitin (Wilkinson et al. 1989). This enzyme is thought to be involved in ubiquitin recycling to maintain the pools of monomeric ubiquitin necessary for proteolysis (Larsen et al. 1998). Johnston et al. (1997) have determined the crystal structure of human UCHL3 and identified active sites.

GGT1 encodes gamma-glutamyltransferase, an enzyme involved in glutathione metabolism (Curthoys and Hughey 1979). Inborn deficiency of GGT1 causes glutathionuria (Schulman et al. 1975; Wright et al. 1980).

TGM1, also known as transglutaminase, is expressed during terminal differentiation of keratinocytes (Candi et al. 1995); this enzyme synthesizes the cornified envelope by a cross-linking reaction (Melino et al. 2000). Mutations in the *TGM1* gene cause a skin disease, lamellar ichthyosis (Huber et al. 1995; Russell et al. 1995).

To investigate in detail the nature of apparent genotype/phenotype correlations among the 19 human genes described above, we began by searching for additional SNPs in their promoter regions, exons, and introns (except for repetitive elements) and report here a total of 680 genetic variations, of which 405 had not previously been reported.

Subjects and methods

After informed consent was obtained from each participant, total genomic DNAs were isolated from peripheral leukocytes of 48 unrelated Japanese individuals by the standard phenol/chloroform extraction method. On the basis of sequence information in the GenBank, we designed polymerase chain reaction (PCR) primers to amplify DNA from all 19 genes in their entirety, except that repetitive elements were excluded by invoking the REPEAT MASKER computer program (http://ftp.genome.washington.edu/cgi-bin/RepeatMasker). PCR experiments and DNA sequencing were performed according to methods described previously (Iida et al. 2001; Saito et al. 2001; Sekine et al. 2001). All SNPs detected by the PolyPhred Computer Program (Nickerson et al. 1997) were confirmed by sequencing both strands of each PCR product.

Results

We defined exon-intron boundaries within each of the 19 genes examined by comparing genomic sequences with cDNA sequences. The accession numbers of the genomic sequences and the cDNA sequences used for this study are listed in Table 1. We screened 96 Japanese chromosomes for SNPs in eight *CYP* genes, and nine esterase genes, plus *GGT1* and *TGM1,* by direct DNA sequencing. The re-sequencing of a total of about 342 kb genomic DNA (153.7 kb for the *CYP* genes, 171.6 kb for esterases, 16.3 kb for the other two genes) identified 607 SNPs (284 in *CYPs*, 302 in esterases, and 21 in the other two genes) and 73 insertion/deletion polymorphisms (35 in *CYPs* and 38 in esterases; Table 2). Among the 680 genetic variations identified in our screening, including insertion/deletion polymorphisms, 405 (60%) had not been reported previously.

CYP genes

Figure 1 illustrates the location of each variation among the *CYP* genes. Detailed information about nucleotide positions and substitutions is summarized in Table 3; the numbers of SNPs are summarized in Table 4. Among the 284 SNPs found in *CYP* genes, 13 were located in 5' flanking regions, 231 in introns, 33 in exons, and seven in 3' flanking regions. Among the SNPs detected in exons, 23 were located in coding regions and ten were in 3'UTRs. Among the former, 15 would cause substitution of an amino acid, and seven of those were novel. Of the eight SNPs that were synonymous, three were novel (Table 5).

Esterase genes

Figure 2 illustrates the location of each variation found among the esterase genes examined; detailed information regarding nucleotide positions and substitutions is summarized in Table 6. Among the 302 SNPs, 21 were located in 5' flanking regions, 252 in introns, 17 in exons, and 12 in 3' flanking regions. Of the 17 SNPs detected in exons, one was located in a 5'UTR; ten were in coding regions, and six were in 3'UTRs. Among the SNPs detected in coding regions, five would substitute an amino acid, and two of those were novel. Among the five synonymous SNPs, three were novel (Table 5).

Other genes

Figure 3 illustrates the location of each variation found in the *GGT1* and *TGM1* genes; detailed information regarding nucleotide positions and substitutions is summarized in Table 7. Among the 21 SNPs, three were located in 5' flanking regions, 13 in introns, and five in exons; three of these five were located in coding regions and the other two in 3'UTRs. Of the three SNPs detected in coding regions, one would cause the substitution of an amino acid, and other two were synonymous SNPs. All three were novel (Table 5).

Discussion

We identified a total of 680 genetic variations (607 SNPs and 73 insertion/deletion polymorphisms) among 19 enzyme-encoding genes selected for this study, by screening DNA from 48 unrelated Japanese individuals with respect to the entire relevant genomic regions except for repetitive sequences. The genes examined included eight cytochrome P450 (*CYP*) genes and nine esterase genes, plus two others. All data for the genetic variations reported here are available on our website (http://snp.ims.u-tokyo.ac.jp/).

CYP enzymes play central roles in the oxidative metabolism of numerous endogenous substrates, such as steroid hormones, and of xenobiotics, including various carcinogens and toxins (Ding and Kaminsky 2002). Among the *CYP* genes examined here, other investigators have previously detected 27 polymorphisms that would affect amino acid sequences [ten in *CYP2A6*, six in *CYP2B6*, three in *CYP2E*, and eight in *TBXAS1*; Human Cytochrome P450 (*CYP*) Allele Nomenclature Committee, http://www.imm.ki.se/CYPalleles/]. Zhang et al. (2002) have detected an additional SNP (Arg257-Cys) in the coding region of *CYP2A13*. However, of the 28 polymorphisms reported previously, we have found only six in our Japanese population sample (Ile471Thr in *CYP2A6*; Arg257Cys in *CYP2A13*; Arg22Cys, Gln172His, and Arg487Cys in *CYP2B6*; Glu450Lys in *TBXAS1*). On the other hand, we have found seven novel non-synonymous substitutions (one in *CYP2A6*, two in *CYP2A13*, two in *TBXAS1*, and two in *CYP7A1*; Table 5). Our results should contribute to a better understanding of ethnic differences in drug responses or possible correlations between genotypes and phenotypes of disease susceptibility.

The promoter region of the *CYP7A1* gene contains a potential binding site for a hepatic-specific transcription factor, CPF (*CYP7A1* promoter binding factor; Nitta et al. 1999). Although mutation of the CPF site abolishes hepatic-specific expression of the gene in transient transfection assays (Nitta et al. 1999), we have failed to find any variant, including insertion/deletion polymorphisms, in the CPF-binding region among the 96 Japanese chromosomes examined.

Although we have found 302 genetic variations among nine esterase genes, only three represent novel changes that would cause substitutions of amino acids (Table 5). In the *AADAC*, *CES1*, *CES2*, and *UCHL3* genes, other research groups have determined presumed active-site residues (Johnston et al. 1997; Pindel et al. 1997; Humerickhouse et al. 2000; Trickett et al. 2001); however, we have found no variations in these regions. As the promoter region of the *AADAC* gene contains a potential response element for aryl hydrocarbons, which could allow the induction of the gene in response to xenobiotics (Trickett et al. 2001), polymorphisms in the 5' flanking region should be investigated intensively.

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