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906 variations among 27 genes encoding cytochrome P450 (CYP) enzymes and aldehyde dehydrogenases (ALDHs) in the Japanese population

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Abstract We screened DNAs from 48 Japanese individuals for single-nucleotide polymorphisms (SNPs) in genes encoding 13 cytochrome P450 (CYP) enzymes and 14 aldehyde dehydrogenases (ALDHs) by directly sequencing their entire genomic regions except for repetitive elements. This approach identified 810 SNPs and 96 insertion/deletion polymorphisms among the 27 genes. Of the 810 SNPs, 229 were identified among the *CYP* genes and 581 in the *ALDH* genes; of the total, 48 SNPs were located in 5' flanking regions, 619 in introns, 91 in exons, and 52 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.

Key words Single-nucleotide polymorphism (SNP) · Cytochrome P450 (CYP) · Aldehyde dehydrogenase (ALDH) · Steroid and xenobiotic receptor/pregnenolone X receptor (SXR/PXR) · Nuclear receptor · Xenobiotic response element · Dioxin-responsive enhancer

Introduction

Cytochrome P450 (CYP) enzymes belong to a superfamily of hemoproteins that play central roles in the oxidative metabolism of numerous endogenous substrates such as

steroid hormones and xenobiotics, including various carcinogens and toxins (Denison and Whitlock 1995; Nelson et al. 1996). *CYP* genes are classified into different families and subfamilies on the basis of sequence similarities.

Polymorphisms have been reported in *CYP1A1*, *CYP1A2*, and *CYP1B1* genes [Human Cytochrome P450 (*CYP*) Allele Nomenclature Committee, <http://www.imm.ki.se/CYPalleles/>]. These three genes are inducible by exposure to agents such as 2,3,7,8-tetrachlorodibenzo-p-dioxin (dioxin; Jaiswal et al. 1985, 1987; Sutter et al. 1994). Two polymorphisms in the *CYP1A1* gene, a T-to-C polymorphism in the 3'-noncoding region and an A-to-G polymorphism (Ile462Val) in exon 7, appear to be associated with susceptibility to lung cancer (Spurr et al. 1987; Hayashi et al. 1991). For its part, *CYP1A2* is expressed in human liver but expression levels vary significantly from one individual to another (Butler et al. 1992). An SNP in its 5' flanking region affects inducibility of this enzyme (Nakajima et al. 1999). Another SNP, in intron 1, was associated with high catalytic activity when subjects were exposed to tobacco smoke (Sachse et al. 1999).

As for *CYP1B1*, a C-to-G polymorphism (Leu432Val) in exon 3 has been associated with estrogen receptor-positive and progesterone receptor-positive breast cancers in Caucasian patients, as well as with prostate cancers in other racial groups (Bailey et al. 1998; Stoilov et al. 1998; Tang et al. 2000). Another polymorphism in this gene, Ala119Ser in exon 2, appears to influence susceptibility to breast cancer and squamous cell carcinoma of the lung in Japanese populations (Watanabe et al. 2000). Mutations in the *CYP1B1* gene are responsible for primary congenital glaucoma (Bejjani et al. 1998; Stoilov et al. 1998; Plasilova et al. 1999).

Members of the *CYP3A* subfamily are the most abundantly expressed *CYPs* in human liver and small intestine (Cholerton et al. 1992). Four *CYP3A* genes, *CYP3A4*, *CYP3A5*, *CYP3A7*, and *CYP3A43*, have been described in humans (Nelson et al. 1996; Finta and Zaphiropoulos 2000; Domanski et al. 2001; Westlind et al. 2001), and polymorphisms have been reported in the first three of those genes

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[Human Cytochrome P450 (CYP) Allele Nomenclature Committee, <http://www.imm.ki.se/CYPalleles/>]. *CYP3A4* is most abundant in adult liver (Wrighton and Stevens. 1992); this enzyme metabolizes approximately 50% of the drugs in current use as well as a number of steroids, environmental chemicals, and carcinogens (Thummel and Wilkinson 1998; Guengerich 1999). Nonsynonymous SNPs in *CYP3A4* have been identified in various ethnic populations (Sata et al. 2000; Dai et al. 2001; Eiselt et al. 2001; Hsieh et al. 2001; Lamba et al. 2002), and Rebbeck et al. (1998) have reported association between an SNP in the 5' flanking region of the *CYP3A4* gene and advanced prostate cancer. Expression levels of *CYP3A4*, *CYP3A5*, and *CYP3A7* vary widely among individuals; measurements of *CYP3A4* activities in adults reveal 10- to 40-fold differences (de Wildt et al. 1999). *CYP3A5* also shows heterogeneity of expression in liver (Lown et al. 1994), and SNPs resulting in alternative splicing and an absence of *CYP3A5* protein have been found in some individuals (Kuehl et al. 2001). *CYP3A7*, on the other hand, is expressed mainly in fetal liver; this enzyme seems to disappear shortly after birth, although some people continue to express *CYP3A7* mRNA even in adulthood (Schuetz et al. 1994).

Animal experiments have revealed an important role of *CYP4B1* in mutagenic activation of procarcinogens in the urinary bladder (Imaoka et al. 1997). Bladder-tumor patients, indeed, show significantly higher expression of *CYP4B1* than do patients with other types of cancer (Imaoka et al. 2000).

CYP4F2, *CYP4F3*, and *CYP4F8* were originally cloned from human neutrophils, liver, and seminal vesicle, respectively (Kikuta et al. 1993, 1994; Bylund et al. 1999). *CYP4F2* and *CYP4F3* are also called leukotriene B₄ (LTB₄) omega-hydroxylases because they possess efficient catalytic activity toward LTB₄, an important chemotactic and chemokinetic participant in the inflammatory response.

CYP27A1 (sterol 27-hydroxylase) catalyzes the first step in oxidation of the side chains of sterol intermediates during synthesis of bile acids (Cali and Russell 1991). Mutations in the *CYP27A1* gene cause cerebrotendinous xanthomatosis, a rare autosomal recessive defect of lipid storage (Cali et al. 1991). *CYP27B1*, also known as 25-hydroxyvitamin D₃ 1alpha-hydroxylase (1alpha-hydroxylase), catalyzes the conversion of 25-hydroxyvitamin D₃ to 1alpha, 25-dihydroxyvitamin D₃. This enzyme plays an important role in calcium homeostasis (Takeyama et al. 1997). Mutations in the *CYP27B1* gene cause pseudovitamin D-deficiency rickets (Fu et al. 1997; Kitanaka et al. 1998; Wang et al. 1998).

The aldehyde dehydrogenase (ALDH; EC 1.2.1.3) superfamily involves a group of NAD (P)⁺-dependent enzymes that catalyze the oxidation of a wide spectrum of endogenous and exogenous aldehydes (Lindahl 1992). Thus far, 17 functional *ALDH* genes and three pseudogenes have been identified in the human genome and some polymorphisms have been reported already (Yoshida et al. 1998; Vasilidou and Pappa 2000; Sophos et al. 2001; Aldehyde Dehydrogenase Gene Superfamily Database, <http://www.uchsc.edu/sp/sp/alcdbase/aldhcov.html>).

The *ALDH1* subfamily consists of five genes, *ALDH1A1*, *ALDH1A2*, *ALDH1A3*, *ALDH1B1*, and *ALDH1L1*. *ALDH1A1* is a cytosolic enzyme ubiquitously distributed in human tissues, including brain and red blood cells (Yoshida 1992). Several *ALDH1A1* variants have been associated with various degrees of enzyme deficiency in the liver and red blood cells (Yoshida et al. 1989; Yoshida 1992). Mitochondrial *ALDH1B1* is expressed in liver, kidney, muscle, heart, and placenta (Stewart et al. 1996); this enzyme may play a role in ethanol detoxification (Stewart et al. 1995). Although three polymorphisms have been reported in its coding regions, no significant difference has been found in the allelic frequencies of those polymorphisms between alcoholic versus nonalcoholic Caucasians (Sherman et al. 1993). *ALDH1A2* is involved in retinal metabolism (Wang et al. 1996). *ALDH1A3* is expressed in salivary gland, stomach, and kidney (Hsu et al. 1994). The *ALDH1L1* gene encodes a 10-formyltetrahydrofolate dehydrogenase (Champion et al. 1994).

ALDH2, a mitochondrial enzyme, is highly expressed in various tissues but predominantly in the liver (Stewart et al. 1996). *ALDH2* exhibits strong oxidative activity toward acetaldehyde, and plays a major role in its detoxification (Lindahl 1992). In oriental populations, alcohol sensitivity is associated with a genetic deficiency of *ALDH2* caused by a G-to-A mutation in exon 12 (Yoshida et al. 1985). A polymorphism in the human *ALDH2* promoter was recently described (Chou et al. 1999; Harada et al. 1999), but it is not clear whether this polymorphism affects alcohol metabolism.

The *ALDH3* subfamily consists of four genes, *ALDH3A1*, *ALDH3A2*, *ALDH3B1*, and *ALDH3B2*. *ALDH3A1* is a cytosolic enzyme highly expressed in stomach and lung, and at low (or undetectable) levels in normal liver (Lindahl 1992). Although a C-to-G polymorphism (Pro329Ala) has been reported in Caucasian and Asian populations (Tsukamoto et al. 1997), its biological effects are currently unknown. *ALDH3A2*, a microsomal enzyme constitutively expressed in several tissues, catalyzes oxidation of fatty aldehydes (Rizzo and Craft 1991; Chang and Yoshida 1997). Mutations in *ALDH3A2* that cause loss of enzymatic activity are responsible for Sjögren-Larsson syndrome (De Laurenzi et al. 1996). Hsu et al. (1997) determined the structures of the *ALDH3B1* and *ALDH3B2* genes, but the function of neither enzyme is known at present.

ALDH5A1 is highly expressed in brain as well as in liver, pituitary, heart, and ovary (Chambliss et al. 1995). Mutations in the *ALDH5A1* gene cause succinic semialdehyde dehydrogenase deficiency, a rare inborn error of the neurotransmitter 4-aminobutyric acid (Chambliss et al. 1998). *ALDH6A1* is the only CoA-dependent dehydrogenase in the ALDH family (Goodwin et al. 1989). Lin and Napoli (2000) isolated a cDNA encoding *ALDH8A1*. Allelic variants of the *ALDH9A1* gene, which encodes an enzyme that catalyzes dehydrogenation of gamma-aminobutyraldehyde to gamma-aminobutyric acid (Kurys et al. 1989), have been reported but not yet characterized (Lin et al. 1996).

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

Gene name	Chromosomal localization	Accession number			
		Genomic sequence		cDNA sequence	
<i>CYP</i>					
<i>CYP1A1</i>	15q22–q24	X04300.1	AC020705.4	K03191.1	NM_000499.1
<i>CYP1A2</i>	15q22–qter	AC020705.4		XM_044660.2	
<i>CYP1B1</i>	2p21	AC009229.4		NM_000104.1	
<i>CYP3A4</i>	7q21.1	AF280107.1		AF182273.1	D11131.1
<i>CYP3A5</i>	7q21.1	AC005020.5		NM_000777.1	
<i>CYP3A7</i>	7q21–q22.1	AF280107.1		NM_000765.1	
<i>CYP3A43</i>	7q21.1	AC011904.3		NM_022820.1	
<i>CYP4B1</i>	1p34–p12	AL356793.10		NM_000779.1	
<i>CYP4F2</i>	19pter–p13.11	AC005336.1		NM_001082.2	AB015295.1
<i>CYP4F3</i>	19p13.2	AD000685.1		NM_000896.1	
<i>CYP4F8</i>	19p13.1	AC068845.3		NM_007253.1	
<i>CYP27A1</i>	2q33–qter	AC009974.7		NM_000784.1	
<i>CYP27B1</i>	12q13.1–q13.3	AC025165.27		NM_000785.2	AB005038.1
<i>ALDH</i>					
<i>ALDH1A1</i>	9q21	AC009284.2	AL162416.3	AF003341.1	AH002598.1
<i>ALDH1A2</i>	15q21.2	AC025431.7	AC012653.8	NM_003888.1	
<i>ALDH1A3</i>	15q26	AC015712.7		NM_000693.1	
<i>ALDH1B1</i>	9p13	AL135785.9		BC001619.1	
<i>ALDH1L1</i>	3q21.3	AC079848.6		XM_002998.3	
<i>ALDH2</i>	12q24.2	AC002996.1	AC003029.2	NM_000690.1	
<i>ALDH3A1</i>	17p11.2	AC005722.1		NM_000691.1	
<i>ALDH3A2</i>	17p11.2	AC005722.1		XM_045060.1	
<i>ALDH3B1</i>	11q13	AC004923.2		NM_000694.1	
<i>ALDH3B2</i>	11q13	AC021987.3		NM_000695.2	
<i>ALDH5A1</i>	6p22	AL031230.1		NM_001080.1	
<i>ALDH6A1</i>	14q24.2	AC005484.2		NM_005589.1	
<i>ALDH8A1</i>	6q24.1–q25.1	AL445190.9	AL021939.1	XM_017324.1	
<i>ALDH9A1</i>	1q22–q23	AL451074.4		NM_000696.1	

To investigate in more detail the nature of apparent genotype/phenotype correlations for some CYP or ALDH enzymes, we began by searching for additional SNPs in the 13 *CYP* genes and 14 *ALDH* genes described earlier, including their promoter regions and introns, except for repetitive elements, and report here a total of 906 genetic variations, of which 627 had not been reported before.

Subjects and methods

Total genomic DNAs were isolated from peripheral leukocytes of 48 unrelated Japanese individuals by the standard phenol/chloroform extraction method. Informed consent was obtained from each participant. On the basis of sequence information in GenBank, we designed polymerase chain reaction (PCR) primers to amplify DNA from all 27 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

Exon–intron boundaries within each of the 27 genes were defined by comparison of genomic sequences with cDNA sequences. 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 13 *CYP* genes and 14 *ALDH* genes by direct DNA sequencing. Re-sequencing a total of about 430 kb of genomic DNA (148.5 kb for the *CYP* genes, 281.6 kb for *ALDHs*) identified 810 SNPs (229 in *CYPs* and 581 in *ALDHs*) and 96 insertion/deletion polymorphisms (31 in *CYPs* and 65 in *ALDHs*) (Tables 2 and 3, respectively). Among the 906 genetic variations identified in our screening, including insertion/deletion polymorphisms, 627 (69%; 157 in *CYPs* and 470 in *ALDHs*) had not been reported previously.

CYP genes

Figure 1 (a–m) illustrates the location of each variation in the *CYP* genes; detailed information about nucleotide positions and substitutions is summarized in Table 4 (a–m). Numbers of SNPs are summarized in Table 5. Among the 229 SNPs, 19 were located in 5' flanking regions, 159 in introns, 40 in exons, and 11 in 3' flanking regions. Among the 40 SNPs detected in exons, 1 was located in the 5'

Table 2. Summary of genetic variations in 13 *CYP* genes

Gene	All genetic variations	SNPs	Insertion/deletion polymorphisms	Novel	Total base pairs sequenced (kb)	Frequency (bp/1SNP)
<i>CYP1A1</i>	12	10	2	10	7.2	720
<i>CYP1A2</i>	9	8	1	5	5.5	688
<i>CYP1B1</i>	21	15	6	8	10.6	707
<i>CYP3A4</i>	8	5	3	4	16.5	3300
<i>CYP3A5</i>	23	20	3	20	18.1	905
<i>CYP3A7</i>	25	21	4	11	16.9	805
<i>CYP3A43</i>	9	4	5	8	15.9	3975
<i>CYP4B1</i>	42	39	3	26	14.5	372
<i>CYP4F2</i>	33	31	2	28	9.0	290
<i>CYP4F3</i>	44	43	1	17	9.1	212
<i>CYP4F8</i>	26	25	1	15	7.2	288
<i>CYP27A1</i>	4	4	0	2	10.1	2525
<i>CYP27B1</i>	4	4	0	3	7.9	1975
Total	260	229	31	157	148.5	(average) 648

SNP, Single-nucleotide polymorphism

Table 3. Summary of genetic variations in 14 *ALDH* genes

Gene	All genetic variations	SNPs	Insertion/deletion polymorphisms	Novel	Total base pairs sequenced (kb)	Frequency (bp/1SNP)
<i>ALDH1A1</i>	41	40	1	14	37.0	925
<i>ALDH1A2</i>	127	108	19	113	50.5	468
<i>ALDH1A3</i>	74	69	5	70	30.7	445
<i>ALDH1B1</i>	11	11	0	7	5.0	455
<i>ALDH1L1</i>	136	128	8	105	36.0	281
<i>ALDH2</i>	12	10	2	8	11.3	1130
<i>ALDH3A1</i>	20	18	2	11	11.8	656
<i>ALDH3A2</i>	26	23	3	18	15.1	657
<i>ALDH3B1</i>	40	39	1	25	14.3	367
<i>ALDH3B2</i>	20	19	1	12	7.4	389
<i>ALDH5A1</i>	49	39	10	27	18.9	485
<i>ALDH6A1</i>	32	29	3	21	11.2	386
<i>ALDH8A1</i>	28	25	3	16	18.1	724
<i>ALDH9A1</i>	30	23	7	23	14.3	622
Total	646	581	65	470	281.6	(average) 485

SNP, Single-nucleotide polymorphism

a Cytochrome P450, subfamily I (aromatic compound-inducible), polypeptide 1 (CYP1A1)

Fig. 1a–m. Locations of single-nucleotide polymorphisms (SNPs) in the *CYP1A1* (a), *CYP1A2* (b), *CYP1B1* (c), *CYP3A4* (d), *CYP3A5* (e), *CYP3A7* (f), *CYP3A43* (g), *CYP4B1* (h), *CYP4F2* (i), *CYP4F3* (j), *CYP4F8* (k), *CYP27A1* (l), and *CYP27B1* (m) genes, indicated by vertical lines. Open boxes represent exons; hatching on the chromosomes indicates unsequenced regions of repetitive elements. ATG and (TGA, TAG, or TAA), Initiation and stop codons, respectively

b Cytochrome P450, subfamily I (aromatic compound-inducible), polypeptide 2 (CYP1A2)

c Cytochrome P450, subfamily I (dioxin-inducible), polypeptide 1 (CYP1B1)

d Cytochrome P450, subfamily IIIA, polypeptide 4 (CYP3A4)

e Cytochrome P450, subfamily IIIA, polypeptide 5 (CYP3A5)

Fig. 1a-m. Continued

f Cytochrome P450, subfamily IIIA, polypeptide 7 (CYP3A7)

g Cytochrome P450, subfamily IIIA, polypeptide 43 (CYP3A43)

h Cytochrome P450, subfamily IVB, polypeptide 1 (CYP4B1)

Fig. 1a-m. Continued

i Cytochrome P450, subfamily IVF, polypeptide 2 (CYP4F2)

j Cytochrome P450, subfamily IVF, polypeptide 3 (CYP4F3)

k Cytochrome P450, subfamily IVF, polypeptide 8 (CYP4F8)

l Cytochrome P450, subfamily XXVIIA, polypeptide 1 (CYP27A1)

Fig. 1a-m. Continued

m Cytochrome P450, subfamily XXVIIIB, polypeptide 1 (CYP27B1)

Fig. 1a–m. Continued

Table 4a. Summary of genetic variations detected in the *CYP1A1* gene

No.	Location	Position ^a	Genetic variation	NCBI SNP ID
1	5' Flanking	–1061	C/G	
2	5' Flanking	–1035	G/A	
3	5' Flanking	–1020	T/G	
4	5' Flanking	–947	G/A	
5	Intron 1	(1326–1334)	(A) _{8–9}	
6	Intron 1	1357	T/C	
7	Intron 1	1590	C/T	
8	Exon 2	160	G/A(Gly45Asp)	
9	Exon 7	131	A/G(Ile462Val) ^b	rs1048943
10	3' Flanking	249	T/C ^c	
11	3' Flanking	(710–720)	(T) _{10–12}	
12	3' Flanking	834	C/T	

CYP1A1, Cytochrome P450, subfamily I (aromatic compound-inducible), polypeptide 1; NCBI, National Center for Biotechnology Information; SNP, single-nucleotide polymorphism; UTR, untranslated region; del, deletion; ins, insertion

^aFor 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)

^bSNP previously reported by Hayashi et al. (1991)

^cSNP previously reported by Spurr et al. (1987)

Table 4b. Summary of genetic variations detected in the *CYP1A2* gene

No.	Location	Position ^a	Genetic variation	NCBI SNP ID
1	Intron 1	103	T/G ^b	rs2069526
2	Intron 1	679	C/A ^{b,c}	rs762551
3	Intron 2	371	C/T	
4	Intron 4	44	G/A	rs2472304
5	Intron 4	206	G/C	
6	Intron 5	(623–648)	(T) _{22–25}	
7	Intron 6	81	T/C	
8	Exon 7	181	A/T(Gln478His)	
9	Exon 7	295	C/T(Asn516Asn)	rs2470890

CYP1A2, Cytochrome P450, subfamily I (aromatic compound-inducible), polypeptide 2

^bSNPs previously reported by Chida et al. (1999)

^cSNP previously reported by Sachse et al. (1999)

untranslated region (UTR), 26 were in coding regions, and 13 were in 3' UTRs. Among the 26 SNPs detected in coding regions, 15 would cause substitution of an amino acid and 5 of those were novel. Among the 11 SNPs that were synonymous, 4 were novel (Table 6).

Table 4c. Summary of genetic variations detected in the *CYP1B1* gene

No.	Location	Position ^a	Genetic variation	NCBI SNP ID
1	5' Flanking	–3669	G/A	
2	5' Flanking	–3188	C/T	rs162556
3	5' Flanking	–3149	G/C	
4	5' Flanking	–1222	G/A	rs2855655
5	5' Flanking	–376	T/C	rs2567207
6	5' Flanking	–265	C/T	rs2567206
7	Intron 1	129	G/A	rs2551188
8	Intron 1	379	C/T	rs2617266
9	Exon 2	143	C/G(Arg48Gly) ^b	rs10012
10	Exon 2	356	G/T(Ala119Ser) ^b	rs1056827
11	Exon 3	251	C/G(Leu432Val) ^{b,c}	rs1056836
12	Exon 3	304	C/T(Asp449Asp) ^d	rs1056837
13	Exon 3	(799–800)	T/ins(3' UTR)	
14	Exon 3	939	A/C(3' UTR)	rs162562
15	Exon 3	1284	G/T(3' UTR)	rs10916
16	Exon 3	1398	A/del(3' UTR)	
17	Exon 3	1468	A/del(3' UTR)	
18	Exon 3	1564	G/A(3' UTR)	rs2855658
19	Exon 3	1762	C/del(3' UTR)	
20	3' Flanking	(2216–2226)	(T) _{10–12}	
21	3' Flanking	2230	A/del	

CYP1B1, Cytochrome P450, subfamily I (dioxin-inducible), polypeptide 1

^bSNPs previously reported by Stoilov et al. (1998)

^cSNP previously reported by Bailey et al. (1998)

^dSNP previously reported by Tang et al. (2000)

Table 4d. Summary of genetic variations detected in the *CYP3A4* gene

No.	Location	Position ^a	Genetic variation	NCBI SNP ID
1	Intron 2	(754–763)	(T) _{9–11}	
2	Intron 7	258	C/T	rs2246709
3	Intron 7	894	C/T	
4	Exon 9	(32–33)	A/ins(Frameshift) ^b	
5	Intron 10	12	G/A	rs2242480
6	Intron 10	459	T/del	
7	Intron 10	608	C/T ^c	
8	Intron 12	2467	A/G	

CYP3A4, Cytochrome P450, subfamily IIIA, polypeptide 4

^bSNP previously reported by Hsieh et al. (2001)

^cSNP previously reported by Dai et al. (2001)

ALDH genes

Figure 2 (a–n) illustrates the location of each variation found in *ALDH* genes; detailed information regarding nucleotide positions and substitutions is summarized in Table 7 (a–n). Numbers of SNPs are summarized in Table 8. Among the 581 *ALDH* SNPs detected in our Japanese sample population, 29 were located in 5' flanking regions, 460 in introns, 51 in exons, and 41 in 3' flanking regions. Of the 51 SNPs detected in exons, 3 were located in 5' UTRs, 29 in coding regions, and 19 in 3' UTRs. Among the 29 SNPs detected in coding regions, 19 would cause substitution of an amino acid and 10 of those were novel. Among the ten synonymous SNPs, three were novel (Table 9).

Table 4e. Summary of genetic variations detected in the *CYP3A5* gene

No.	Location	Position ^a	Genetic variation	NCBI SNP ID
1	Exon 1	69	T/C(5' UTR)	
2	Intron 1	(955–956)	A/ins	
3	Intron 1	1126	A/G	
4	Intron 1	1145	T/G	
5	Intron 1	1543	C/A	
6	Intron 1	2366	G/A	
7	Intron 3	1617	G/A ^b	rs776746
8	Intron 4	1813	G/A	
9	Intron 4	1887	A/T	
10	Intron 4	3384	C/T	
11	Intron 4	3415	T/C	
12	Intron 4	3760	G/A	
13	Intron 4	3885	C/T	
14	Intron 4	5061	A/del	
15	Intron 4	5316	A/T	
16	Intron 9	77	G/T	
17	Intron 9	347	A/G	rs1419745
18	Intron 9	1791	C/T	
19	Intron 12	1408	A/del	
20	Exon 13	110	T/C(3' UTR)	rs15524
21	3' Flanking	542	T/C	
22	3' Flanking	737	T/G	
23	3' Flanking	804	A/C	

CYP3A5, Cytochrome P450, subfamily IIIA, polypeptide 5

^bSNP previously reported by Kuehl et al. (2001)**Table 4f.** Summary of genetic variations detected in the *CYP3A7* gene

No.	Location	Position ^a	Genetic variation	NCBI SNP ID
1	5' Flanking	–1680	C/A	
2	5' Flanking	–1191	A/C	
3	Intron 1	1173	G/A	
4	Intron 1	1597	T/C	
5	Intron 1	1604	C/A	rs2687134
6	Intron 2	8113	C/T	rs2687142
7	Intron 2	8214	A/G	rs2687143
8	Intron 3	762	T/C	
9	Intron 3	1111	A/G	rs2687144
10	Intron 3	1275	C/T	rs2687145
11	Intron 5	163	C/T	rs2687075
12	Intron 7	(1060–1069)	(T) _{9–10}	
13	Intron 8	628	T/C	rs2037498
14	Intron 10	1091	T/C	rs2687076
15	Exon 11	200	C/G(Thr409Arg)	rs2257401
16	Intron 11	92	A/G	rs2687077
17	Intron 11	337	A/C	rs1403196
18	Intron 11	(592–594)	AAG/del	
19	Intron 12	817	T/A	rs2687079
20	Intron 12	911	C/T	
21	Intron 12	1137	T/del	
22	Intron 12	2147	T/del	
23	Exon 13	125	T/C(3' UTR)	rs12360
24	Exon 13	218	A/C(3' UTR)	
25	Exon 13	225	A/G(3' UTR)	rs10211

CYP3A7, Cytochrome P450, subfamily IIIA, polypeptide 7

Table 4g. Summary of genetic variations detected in the *CYP3A43* gene

No.	Location	Position ^a	Genetic variation	NCBI SNP ID
1	Intron 1	3579	T/del	
2	Intron 2	2029	C/T	rs800672
3	Intron 2	2427	T/del	
4	Intron 3	3034	T/C	
5	Intron 3	3433	T/del	
6	Intron 3	3504	T/C	
7	Intron 4	2767	A/del	
8	Exon 5	22	G/A(Leu114Leu)	
9	Intron 12	(1585–1584)	A/ins	

CYP3A43, Cytochrome P450, subfamily IIIA, polypeptide 43

Table 4h. Summary of genetic variations detected in the *CYP4B1* gene

No.	Location	Position ^a	Genetic variation	NCBI SNP ID
1	5' Flanking	–609	G/A	rs632645
2	5' Flanking	–537	T/C	rs632233
3	5' Flanking	–333	A/T	
4	5' Flanking	–18	G/T	rs2297813
5	Intron 1	341	C/T	
6	Intron 1	542	C/T	
7	Intron 1	2856	G/A	
8	Intron 1	(2923–2938)	(GT) _{7–8}	
9	Intron 1	3101	A/G	rs681840
10	Intron 1	4352	C/T	rs751027
11	Intron 1	4398	A/T	rs837395
12	Intron 1	6086	G/T	
13	Intron 1	6598	G/A	
14	Intron 1	6660	A/G	
15	Intron 1	7242	T/C	rs2405335
16	Intron 1	7460	G/A	rs1572603
17	Intron 1	7802	G/A	rs1890251
18	Intron 1	7842	A/G	rs1890250
19	Intron 2	107	C/G	rs2297812
20	Intron 3	361	C/T	
21	Intron 4	–492	C/A	
22	Intron 4	–315	A/G	
23	Intron 4	–157	T/C	
24	Exon 5	22	C/T(Arg173Trp) ^b	
25	Intron 5	125	G/A	
26	Intron 5	(287–289)	CCT/del	
27	Intron 6	54	C/T	rs2297811
28	Intron 7	(99–100)	TC/ins	
29	Exon 8	114	G/A(Met331Ile) ^b	rs2297810
30	Exon 8	139	C/T(Arg340Cys) ^b	
31	Intron 8	247	C/T	
32	Intron 8	366	A/G	
33	Intron 8	650	C/A	
34	Intron 8	844	C/A	
35	Intron 8	1767	G/T	
36	Exon 9	53	C/T(Arg375Cys) ^b	rs2297809
37	Intron 9	652	G/T	
38	Intron 9	774	C/T	
39	Intron 10	33	G/T	
40	Exon 12	224	C/A(3' UTR)	
41	Exon 12	270	G/A(3' UTR)	
42	3' Flanking	129	G/A	

CYP4B1, Cytochrome P450, subfamily IVB, polypeptide 1

^bSNPs previously reported in the *CYP4B1* allele nomenclature (<http://www.imm.ki.se/CYPalleles/cyp4b1.htm>)

Table 4i. Summary of genetic variations detected in the *CYP4F2* gene

No.	Location	Position ^a	Genetic variation	NCBI SNP ID	No.	Location	Position ^a	Genetic variation	NCBI SNP ID
1	Intron 1	(145–146)	CA/del		18	Intron 3	1945	T/A	
2	Intron 1	193	C/T		19	Intron 3	2621	G/A	
3	Intron 1	324	T/C		20	Intron 3	2665	A/G	
4	Intron 1	367	G/C		21	Intron 6	194	G/T	
5	Intron 1	402	T/C		22	Intron 7	67	G/A	
6	Exon 2	35	T/G(Trp12Gly)		23	Intron 7	2811	T/G	rs2074901
7	Exon 2	166	A/G(Pro55Pro)		24	Intron 7	(3096–3097)	G/ins	
8	Intron 2	125	A/G	rs2074902	25	Intron 8	145	G/A	
9	Intron 2	440	T/C		26	Exon 9	44	C/T(His343His)	rs2074900
10	Exon 3	48	C/T(Ala82Ala)		27	Exon 11	48	G/A(Val433Met)	rs2108622
11	Intron 3	701	T/A		28	Intron 12	108	C/T	
12	Intron 3	742	G/A		29	Intron 12	285	A/T	
13	Intron 3	1020	G/A		30	Exon 13	238	C/A(3' UTR)	
14	Intron 3	1039	C/A		31	Exon 13	342	G/A(3' UTR)	
15	Intron 3	1040	C/G		32	Exon 13	563	T/C(3' UTR)	
16	Intron 3	1516	G/T	rs2006193	33	Exon 13	707	G/C(3' UTR)	
17	Intron 3	1920	G/C						

CYP4F2, Cytochrome P450, subfamily IVF, polypeptide 2

Table 4j. Summary of genetic variations detected in the *CYP4F3* gene

No.	Location	Position ^a	Genetic variation	NCBI SNP ID	No.	Location	Position ^a	Genetic variation	NCBI SNP ID
1	5' Flanking	–141	C/T	rs1290616	23	Intron 7	2107	T/del	
2	Intron 1	142	T/G	rs1290617	24	Intron 7	2255	T/A	rs2733749
3	Intron 2	227	C/G	rs1291619	25	Intron 8	132	A/C	rs2733750
4	Intron 2	258	G/T		26	Exon 9	59	G/A(Pro348Pro)	rs1805041
5	Intron 2	351	C/T	rs1290620	27	Exon 9	89	A/G(Val358Val)	rs1805042
6	Intron 2	916	C/T		28	Intron 9	13	G/A	
7	Intron 2	918	T/C	rs1290621	29	Intron 9	36	G/C	rs2683039
8	Intron 2	3019	C/T	rs759998	30	Intron 9	167	C/G	rs2683040
9	Intron 2	3417	C/T	rs2077040	31	Intron 9	368	T/C	rs659447
10	Intron 2	4090	G/A	rs2280748	32	Intron 9	369	G/A	rs2683045
11	Intron 3	89	G/A		33	Intron 9	458	T/C	
12	Intron 3	243	C/T		34	Intron 10	46	A/C	
13	Intron 3	298	T/C	rs1290624	35	Intron 10	63	C/A	
14	Intron 3	483	G/A	rs1290625	36	Intron 11	14	C/G	
15	Intron 3	502	G/C	rs2280749	37	Intron 11	84	G/A	
16	Intron 3	755	A/T	rs2280750	38	Intron 11	113	T/C	
17	Intron 3	855	G/A	rs2072598	39	Intron 11	164	T/G	
18	Intron 3	970	C/T	rs2073600	40	Intron 11	165	T/C	
19	Intron 4	12	C/T	rs1290626	41	Intron 12	6	G/A	rs1915390
20	Exon 6	84	G/A(Leu203Leu)	rs1053037	42	Intron 12	156	G/A	
21	Intron 6	122	C/T	rs2283612	43	Intron 12	253	T/G	
22	Exon 7	159	C/A(Ala269Asp)		44	Intron 12	346	A/C	rs2683057

CYP4F3, Cytochrome P450, subfamily IVF, polypeptide 3

Table 4k. Summary of genetic variations detected in the *CYP4F8* gene

No.	Location	Position ^a	Genetic variation	NCBI SNP ID	No.	Location	Position ^a	Genetic variation	NCBI SNP ID
1	5' Flanking	–61	G/T		14	Intron 8	222	C/G	
2	Exon 1	67	G/T(Leu20Leu)		15	Intron 8	334	A/T	
3	Intron 1	707	T/G		16	Intron 8	1999	T/C	
4	Intron 1	857	G/A		17	Intron 8	4184	C/T	
5	Intron 1	907	G/A		18	Exon 9	119	C/T(Arg412Stop)	
6	Intron 2	101	C/G	rs714772	19	Intron 9	29	C/T	rs2056820
7	Intron 2	409	C/G	rs714773	20	Intron 9	70	C/T	rs2056821
8	Intron 2	668	T/C		21	Exon 11	27	C/A(Pro447Pro)	rs2056822
9	Intron 2	818	G/A		22	Intron 11	282	G/C	rs2239365
10	Intron 2	1079	C/T	rs2072599	23	Intron 11	340	C/T	rs2239366
11	Intron 2	1194	C/A		24	3' Flanking	35	T/C	
12	Intron 5	45	G/T	rs2072601	25	3' Flanking	83	G/C	rs2239367
13	Exon 8	(19–20)	GCCAG/ins		26	3' Flanking	90	A/G	rs2283605

CYP4F8, Cytochrome P450, subfamily IVF, polypeptide 8

Table 4l. Summary of genetic variations detected in the *CYP27A1* gene

No.	Location	Position ^a	Genetic variation	NCBI SNP ID
1	Intron 1	295	A/G	rs19753
2	Intron 1	4189	G/T	
3	Intron 1	17503	C/T	rs736312
4	3' Flanking	131	C/T	

CYP27A1, Cytochrome P450, subfamily XXVIIA, polypeptide 1

Table 4m. Summary of genetic variations detected in the *CYP27B1* gene

No.	Location	Position ^a	Genetic variation	NCBI SNP ID
1	5' Flanking	−1794	C/T	rs703842
2	Intron 6	173	C/T	
3	Intron 8	113	A/C	
4	3' Flanking	1081	G/C	

CYP27B1, Cytochrome P450, subfamily XXVIIIB, polypeptide 1

Table 5. Number and regions of SNPs detected in 13 *CYP* genes

				Exon				
Gene	5' Flanking	Intron	3' Flanking	5' UTR	Coding		3' UTR	Total
					Nonsynonymous	Synonymous		
<i>CYP1A1</i>	4	2	2	0	2	0	0	10
<i>CYP1A2</i>	0	6	0	0	1	1	0	8
<i>CYP1B1</i>	6	2	0	0	3	1	3	15
<i>CYP3A4</i>	0	5	0	0	0	0	0	5
<i>CYP3A5</i>	0	15	3	1	0	0	1	20
<i>CYP3A7</i>	2	15	0	0	1	0	3	21
<i>CYP3A43</i>	0	3	0	0	0	1	0	4
<i>CYP4B1</i>	4	28	1	0	4	0	2	39
<i>CYP4F2</i>	0	22	0	0	2	3	4	31
<i>CYP4F3</i>	1	38	0	0	1	3	0	43
<i>CYP4F8</i>	1	18	3	0	1	2	0	25
<i>CYP27A1</i>	0	3	1	0	0	0	0	4
<i>CYP27B1</i>	1	2	1	0	0	0	0	4
Total	19	159	11	1	15	11	13	229

SNP, Single-nucleotide polymorphism; UTR, untranslated region

Table 6. Novel SNPs detected in exons of 13 *CYP* genes

Region	Gene	Location	Position	SNP
5' UTR	<i>CYP3A5</i>	Exon 1	69	T/C
Coding	Nonsynonymous	<i>CYP1A1</i>	Exon 2	160
		<i>CYP1A2</i>	Exon 7	181
Synonymous		<i>CYP4F2</i>	Exon 2	35
		<i>CYP4F3</i>	Exon 7	159
		<i>CYP4F8</i>	Exon 9	119
		<i>CYP3A43</i>	Exon 5	22
		<i>CYP4F2</i>	Exon 2	166
			Exon 3	48
		<i>CYP4F8</i>	Exon 1	67
		<i>CYP3A7</i>	Exon 13	218
		<i>CYP4B1</i>	Exon 12	224
			Exon 12	270
3' UTR	<i>CYP4F2</i>	Exon 13	238	G/A
		Exon 13	342	G/A
		Exon 13	563	T/C
		Exon 13	707	G/C

SNP, Single-nucleotide polymorphism; UTR, untranslated region

a Aldehyde dehydrogenase 1 family, member A1 (ALDH1A1)

b Aldehyde dehydrogenase 1 family, member A2 (ALDH1A2)

Fig. 2a–n. Locations of SNPs in the *ALDH1A1* (a), *ALDH1A2* (b), *ALDH1A3* (c), *ALDH1B1* (d), *ALDH1L1* (e), *ALDH2* (f), *ALDH3A1* (g), *ALDH3A2* (h), *ALDH3B1* (i), *ALDH3B2* (j), *ALDH5A1* (k), *ALDH6A1* (l), *ALDH8A1* (m), and *ALDH9A1* (n) genes, indicated by vertical lines. Open boxes represent exons; hatching on the chromosomes indicates regions of repetitive elements. ATG and (TGA, TAG, or TAA), Initiation and stop codons, respectively

c Aldehyde dehydrogenase 1 family, member A3 (ALDH1A3)

d Aldehyde dehydrogenase 1 family, member B1 (ALDH1B1)

Fig. 2a–n. Continued

Discussion

We identified a total of 906 genetic variations (810 SNPs and 96 insertion/deletion polymorphisms) by screening DNA from 48 unrelated Japanese individuals in the entire genomic regions, except for repetitive sequences, encoding 13 *CYP* and 14 *ALDH* genes. All data on these SNPs are available on our website (<http://snp.ims.u-tokyo.ac.jp/>).

Cytochrome P450 (*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 (Denison and Whitlock 1995; Nelson et al. 1996). Others had detected 30 polymorphisms that would affect amino acid sequences (3 in *CYP1A1*, 5 in *CYP1A2*, 18 in *CYP3A4*, and 4 in *CYP3A5*) (Cascorbi et al. 1996; Jounaidi et al. 1996; Huang et al. 1999;

Sata et al. 2000; Chevalier et al. 2001a,b; Chou et al. 2001; Dai et al. 2001; Eiselt et al. 2001; Hsieh et al. 2001; Hustert et al. 2001; Lamba et al. 2002). However, among the 30 polymorphisms reported previously, we could find in our Japanese subjects only one, an ins/del polymorphism in *CYP3A4*, that causes a frameshift and results in early termination of translation at exon 9. This polymorphism was also reported in the Chinese population (Hsieh et al. 2001). On the other hand, we were able to find two novel nonsynonymous substitutions (Gly45Asp in *CYP1A1* and Gln478His in *CYP1A2*). These results indicated that archived polymorphisms may be very rare substitutions or limited to specific ethnic groups.

In the 5' flanking region of the *CYP1A1* gene, we identified putative xenobiotic response elements, which control expression of this enzyme (Corchero et al. 2001). A 3-kb 5' flanking portion of the human *CYP1B1* gene also

e Formyltetrahydrofolate dehydrogenase (ALDH1L1, FTHFD)

Fig. 2a-n. Continued

f Aldehyde dehydrogenase 2 family (ALDH2)

g Aldehyde dehydrogenase 3 family, member A1 (ALDH3A1)

h Aldehyde dehydrogenase 3 family, member A2 (ALDH3A2)

i Aldehyde dehydrogenase 3 family, member B1 (ALDH3B1)

Fig. 2a–n. Continued

j Aldehyde dehydrogenase 3 family, member B2 (ALDH3B2)

k Aldehyde dehydrogenase 5 family, member A1 (ALDH5A1)

l Aldehyde dehydrogenase 6 family, member A1 (ALDH6A1)

Fig. 2a–n. Continued

m Aldehyde dehydrogenase 8 family, member A1 (ALDH8A1)

n Aldehyde dehydrogenase 9 family, member A1 (ALDH9A1)

Fig. 2a–n. Continued

Table 7a. Summary of genetic variations detected in the *ALDH1A1* gene

No.	Location	Position ^a	Genetic variation	NCBI SNP ID	No.	Location	Position ^a	Genetic variation	NCBI SNP ID
1	5' Flanking	–851	C/T	rs348445	22	Intron 3	1757	T/A	rs2288087
2	Intron 1	564	T/C		23	Intron 5	90	C/A	rs2303317
3	Intron 1	710	C/T		24	Intron 6	213	T/C	rs2161811
4	Intron 1	–5704	A/G	rs595958	25	Intron 6	1323	C/T	
5	Intron 1	–4648	G/A	rs647880	26	Intron 7	638	C/A	
6	Intron 1	–4399	A/C	rs1424481	27	Intron 8	312	T/C	rs610529
7	Intron 1	–3868	C/G	rs2309779	28	Intron 9	1282	G/C	rs348457
8	Intron 2	2114	G/C	rs1330286	29	Intron 9	(1462–1463)	T/ins	
9	Intron 2	2933	T/C	rs2210103	30	Intron 9	1757	A/G	
10	Intron 2	–1677	A/G	rs348463	31	Intron 9	1948	A/G	rs348458
11	Intron 2	–1646	C/T		32	Intron 10	995	C/T	rs348475
12	Intron 2	–1234	G/C	rs348462	33	Intron 10	2089	A/C	rs63319
13	Exon 3	54	C/T(Ser75Ser)	rs13959	34	Intron 12	899	T/C	rs348471
14	Intron 3	157	T/G		35	Intron 12	1623	C/G	rs1888202
15	Intron 3	339	G/A		36	Intron 12	–1383	T/G	
16	Intron 3	655	C/A		37	3' Flanking	40	T/C	
17	Intron 3	725	T/A	rs348461	38	3' Flanking	132	G/A	rs348485
18	Intron 3	735	C/A		39	3' Flanking	261	T/C	rs348484
19	Intron 3	863	G/A		40	3' Flanking	1150	A/G	rs348481
20	Intron 3	1404	G/A	rs2017362	41	3' Flanking	1864	A/G	rs348480
21	Intron 3	1496	A/T	rs722921					

ALDH1A1, Aldehyde dehydrogenase 1 family, member A1; NCBI, National Center for Biotechnology Information; SNP, single-nucleotide polymorphism; UTR, untranslated region; del, deletion; ins, insertion

^aFor 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 7b. Summary of genetic variations detected in the *ALDH1A2* gene

No.	Location	Position ^a	Genetic variation	NCBI SNP ID	No.	Location	Position ^a	Genetic variation	NCBI SNP ID
1	5' Flanking	-716	C/G		65	Intron 4	8090	C/T	
2	Intron 1	314	G/del		66	Intron 4	8466	A/C	rs1372369
3	Intron 1	(664-675)	(T) ₁₁₋₁₃		67	Intron 4	12823	C/T	
4	Intron 1	1370	A/G	rs2414530	68	Intron 4	12939	T/C	
5	Intron 1	1557	A/del		69	Intron 4	13108	A/G	rs1441829
6	Intron 1	1934	C/G		70	Intron 4	14935	T/G	
7	Intron 1	(1971-1980)	(T) ₉₋₁₁		71	Intron 4	15321	C/T	
8	Intron 1	2295	T/C		72	Intron 4	15412	T/G	
9	Intron 1	2387	C/T		73	Intron 5	287	G/A	rs1899355
10	Intron 1	2841	T/del		74	Intron 5	1888	G/T	
11	Intron 1	3035	A/G		75	Intron 7	9166	G/A	
12	Intron 1	3319	T/del		76	Intron 7	9914	C/T	
13	Intron 1	3474	T/C		77	Intron 7	18942	G/A	
14	Intron 1	4186	G/C		78	Intron 7	19820	A/G	
15	Intron 1	4222	A/G		79	Intron 7	19826	G/A	
16	Intron 1	4254	T/del		80	Intron 7	19913	A/G	
17	Intron 1	4397	A/G		81	Intron 7	(20110-20111)	ACTA/ins	
18	Intron 1	5935	T/C		82	Intron 7	21857	A/T	
19	Intron 1	6206	T/G		83	Intron 7	21929	A/G	
20	Intron 1	9559	C/T		84	Intron 7	23308	G/T	
21	Intron 1	(9631-9632)	AAGA/ins		85	Intron 7	23554	C/T	
22	Intron 1	9783	G/T	rs1994927	86	Intron 7	(23701-23703)	GTG/del	
23	Intron 1	12731	T/A	rs2704218	87	Intron 7	26479	T/C	
24	Intron 1	13442	G/A		88	Intron 7	26561	T/C	
25	Intron 1	(14173-14176)	AAAA/del		89	Intron 7	26662	C/T	
26	Intron 1	14586	C/G		90	Intron 8	76	G/A	
27	Intron 1	14595	A/G		91	Intron 8	(700-711)	(T) ₁₁₋₁₂	
28	Intron 1	14711	A/G		92	Intron 8	724	T/C	
29	Intron 1	(15327-15337)	(T) ₉₋₁₁		93	Intron 8	800	C/A	
30	Intron 1	17258	A/G		94	Intron 8	1251	G/A	rs2414527
31	Intron 1	17660	A/G	rs1874158	95	Intron 8	1627	G/A	
32	Intron 1	17711	T/C	rs1874157	96	Exon 9	141	G/A(Val348Ile)	
33	Intron 1	18277	A/G		97	Intron 9	778	T/C	
34	Intron 1	18734	T/A		98	Intron 9	801	A/G	
35	Intron 1	19081	C/T		99	Intron 9	868	T/C	
36	Intron 1	21514	G/A		100	Intron 9	1338	A/G	rs2119859
37	Intron 1	21732	A/G		101	Intron 10	(227-229)	TTA/del	
38	Intron 1	21865	C/T		102	Intron 10	316	T/C	
39	Intron 1	26282	A/del		103	Intron 10	368	G/A	
40	Intron 1	27805	T/C		104	Intron 10	660	G/A	
41	Intron 1	28204	C/G		105	Intron 11	104	C/T	
42	Intron 1	28521	T/C		106	Intron 11	229	A/G	
43	Intron 1	49478	G/T	rs2642632	107	Intron 12	117	C/T	
44	Intron 1	49834	G/T		108	Intron 12	691	A/G	
45	Intron 1	50351	C/G		109	Intron 12	1934	T/C	
46	Intron 1	51181	C/T		110	Intron 12	1973	T/A	
47	Intron 3	654	G/A		111	Intron 12	2722	C/A	
48	Intron 3	668	C/T		112	Intron 12	3855	T/C	
49	Intron 3	712	G/T		113	Intron 12	4185	T/C	
50	Intron 3	1273	T/A		114	Intron 12	4991	A/G	
51	Intron 3	1743	C/T		115	Intron 12	(5018-5019)	G/ins	
52	Intron 3	2891	A/G		116	Intron 12	(5051-5052)	A/ins	
53	Intron 3	2919	G/A		117	Intron 12	(5300-5302)	CCT/del	
54	Intron 3	3054	G/C		118	Intron 12	5405	G/C	
55	Intron 4	290	T/C		119	Intron 12	5435	C/A	
56	Intron 4	380	T/C		120	3' Flanking	449	T/C	
57	Intron 4	461	G/T		121	3' Flanking	597	A/C	
58	Intron 4	506	G/A		122	3' Flanking	669	T/C	
59	Intron 4	1952	C/G		123	3' Flanking	763	T/G	rs1063666
60	Intron 4	2079	C/T		124	3' Flanking	1122	T/G	
61	Intron 4	2519	C/G		125	3' Flanking	1336	A/G	rs1061278
62	Intron 4	(2840-2851)	(T) ₁₁₋₁₃		126	3' Flanking	1379	A/T	rs9325
63	Intron 4	7231	A/T		127	3' Flanking	2214	T/C	
64	Intron 4	7958	C/T						

ALDH1A2, Aldehyde dehydrogenase 1 family, member A2

Table 7c. Summary of genetic variations detected in the *ALDH1A3* gene

No.	Location	Position ^a	Genetic variation	NCBI SNP ID	No.	Location	Position ^a	Genetic variation	NCBI SNP ID
1	5' Flanking	-1425	C/T		38	Intron 8	2384	C/A	
2	5' Flanking	-1379	C/T		39	Intron 9	24	A/C	
3	5' Flanking	-1270	T/A		40	Intron 9	91	T/C	
4	5' Flanking	-(1214-1213)	GGA/ins		41	Intron 9	219	C/G	
5	5' Flanking	-1103	C/T		42	Intron 9	435	G/A	
6	Intron 1	986	T/G		43	Intron 9	1472	C/T	
7	Intron 1	1462	G/A		44	Intron 9	2038	G/A	
8	Intron 1	1661	G/A		45	Intron 9	2124	G/A	
9	Intron 1	2360	A/G		46	Intron 9	2154	G/C	
10	Intron 1	2516	G/A		47	Intron 9	2197	G/A	
11	Intron 1	2624	C/T		48	Intron 9	2466	C/T	
12	Intron 1	3255	G/C		49	Intron 9	3655	C/T	
13	Intron 1	(3643-3656)	(T) ₁₂₋₁₄		50	Intron 9	3954	C/G	
14	Intron 1	4265	T/C		51	Exon 10	88	A/G(Met386Val)	
15	Intron 1	5187	C/T		52	Intron 10	8	G/A	
16	Intron 2	43	G/T		53	Intron 10	307	A/C	
17	Intron 2	127	T/C		54	Intron 10	378	G/A	
18	Intron 2	(285-300)	(T) ₁₆₋₁₇		55	Intron 10	975	C/G	
19	Intron 2	778	A/G		56	Intron 10	1088	C/T	
20	Intron 2	1216	A/C		57	Intron 11	105	A/G	
21	Intron 3	81	A/C		58	Intron 11	274	T/G	
22	Intron 3	236	T/G		59	Intron 11	1088	T/A	
23	Intron 3	1467	G/T		60	Intron 12	96	G/A	
24	Intron 3	1725	A/G		61	Intron 12	1537	G/T	
25	Intron 3	3777	A/G		62	Intron 12	1660	C/del	
26	Intron 3	3829	G/C		63	Intron 12	5642	T/C	
27	Intron 3	4299	G/A		64	Exon 13	104	G/C(3' UTR)	
28	Intron 4	84	C/G		65	Exon 13	281	C/T(3' UTR)	
29	Intron 4	126	A/G		66	Exon 13	935	G/A(3' UTR)	rs1130738
30	Intron 6	(290-291)	G/ins		67	Exon 13	1412	G/A(3' UTR)	rs14226
31	Intron 6	705	T/G		68	Exon 13	1878	C/T(3' UTR)	rs7045
32	Intron 7	56	C/T		69	Exon 13	1879	G/A(3' UTR)	rs1802603
33	Intron 7	1107	A/G		70	3' Flanking	743	G/A	
34	Intron 7	1610	C/G		71	3' Flanking	1145	A/G	
35	Intron 7	1820	T/C		72	3' Flanking	1185	T/C	
36	Intron 8	963	C/T		73	3' Flanking	1600	T/C	
37	Intron 8	1824	G/A		74	3' Flanking	1847	C/G	

ALDH1A3, Aldehyde dehydrogenase 1 family, member A3

Table 7d. Summary of genetic variations detected in the *ALDH1B1* gene

No.	Location	Position ^a	Genetic variation	NCBI SNP ID
1	Intron 1	134	C/T	
2	Intron 1	367	A/G	
3	Intron 1	405	C/T	
4	Intron 1	2002	C/T	
5	Intron 1	2157	G/T	
6	Exon 2	192	T/C(Thr61Thr) ^b	rs2073477
7	Exon 2	265	C/T(Ala86Val) ^b	rs2228093
8	Exon 2	329	G/T(Arg107Leu) ^b	rs2073478
9	Exon 2	614	C/T(Thr202Ile)	
10	Exon 2	1619	C/G(3' UTR)	rs3043
11	3' Flanking	168	G/A	

ALDH1B1, Aldehyde dehydrogenase 1 family, member B1

^bSNPs previously reported by Sherman et al. (1993)

contains multiple core recognition motifs for binding to dioxin-responsive enhancer and Sp1 elements (Tang et al. 1996). We found four SNPs (-1061, -1035, -1020, and -947) in this region of *CYP1A1*, and three (-1222, -376, and -265) in *CYP1B1* that might influence transcriptional efficiencies.

Nuclear receptor steroid and xenobiotic receptor/pregnenolone X receptor (SXR/PXR) binds to a PXR response element present in *CYP3A* promoters and activates *CYP3A* genes (Goodwin et al. 1999; Xie et al. 2000). Because expression levels of *CYP3A* differ widely among individuals and the promoters contain multiple putative transcription-factor-binding sites, polymorphisms in the 5' flanking regions have been investigated intensively (Paulussen et al. 2000; Hustert et al. 2001; Kuehl et al. 2001). However, we found only two SNPs in the *CYP3A7* promoter region in the Japanese population by screening a 2-kb segment of 5' flanking DNA.

ALDH genes are considered general detoxifying enzymes that eliminate biogenic and xenobiotic aldehydes (Lindahl 1992). Although 17 functional *ALDH* genes and three pseudogenes have been identified already in the human genome, biological functions of some *ALDH*s remain unclear (Yoshida et al. 1998; Sophos et al. 2001; Vasiliou and Pappa 2000). Polymorphisms in *ALDH* genes are ethnically diverse; previously reported polymorphisms (Glu479Lys in *ALDH2*, Gly214Tyr in *ALDH3A2*, Cys115Ser in *ALDH9A1*) (Novoradovsky et al. 1995; De

Table 7e. Summary of genetic variations detected in the *ALDH1L1* gene

No.	Location	Position ^a	Genetic variation	NCBI SNP ID	No.	Location	Position ^a	Genetic variation	NCBI SNP ID
1	Intron 1	252	G/C		69	Intron 13	299	A/G	
2	Intron 1	544	C/T		70	Intron 13	513	C/T	rs1562475
3	Intron 1	-6596	C/G		71	Intron 13	811	A/G	rs1317682
4	Intron 1	-6513	G/A		72	Intron 13	989	C/T	rs2002287
5	Intron 1	-6478	G/A		73	Intron 14	35	G/A	rs873696
6	Intron 2	240	A/G		74	Intron 14	121	A/G	rs2365002
7	Intron 2	1326	G/C		75	Intron 14	155	T/C	rs1868125
8	Intron 3	217	T/A	rs1868138	76	Intron 14	167	C/T	rs2365003
9	Intron 3	386	G/A		77	Intron 14	205	A/C	
10	Intron 4	271	G/C		78	Intron 14	219	C/G	
11	Intron 4	356	C/T		79	Intron 14	356	T/C	rs1868126
12	Intron 4	608	A/C		80	Intron 14	423	G/A	rs1868127
13	Intron 4	664	A/G		81	Intron 14	467	A/G	rs1868128
14	Intron 4	785	C/G		82	Intron 14	633	T/A	rs1868129
15	Intron 4	874	T/G		83	Intron 14	2275	T/C	
16	Intron 4	1349	G/A		84	Intron 14	2431	C/G	
17	Intron 4	1799	G/A	rs2276731	85	Intron 14	2660	C/T	
18	Intron 4	1815	G/A		86	Intron 14	2740	T/C	
19	Intron 5	272	A/G		87	Intron 14	2756	T/C	
20	Intron 5	301	G/A		88	Intron 14	2805	T/C	
21	Intron 5	343	G/A		89	Intron 14	(3636-3637)	G/ins	
22	Intron 6	926	C/T		90	Intron 14	4347	C/T	rs2278756
23	Exon 7	41	T/C(Leu254Pro)		91	Intron 15	380	A/G	
24	Intron 7	305	C/T		92	Intron 15	(1055-1056)	C/ins	
25	Intron 7	837	C/T		93	Intron 17	15	G/C	
26	Intron 7	866	C/T		94	Intron 17	44	C/T	
27	Intron 7	884	C/T		95	Intron 17	51	G/A	
28	Intron 7	1118	G/C		96	Intron 17	-(2224-2223)	CT/del	
29	Intron 7	1168	G/A		97	Intron 18	140	G/A	rs2290053
30	Intron 7	1451	T/C	rs2166766	98	Intron 19	(51-52)	GC/del	
31	Intron 7	1489	T/C		99	Intron 19	399	C/A	
32	Intron 7	1579	G/A		100	Intron 19	608	A/G	
33	Intron 7	1691	A/C		101	Intron 19	(669-670)	C/ins	
34	Intron 8	1632	T/C		102	Intron 19	1794	G/C	
35	Intron 8	1799	G/C		103	Intron 19	1969	G/T	
36	Intron 8	1986	G/T		104	Intron 19	1972	A/G	
37	Intron 8	2002	A/G		105	Intron 19	2083	G/T	
38	Intron 8	2627	C/T		106	Intron 19	2119	C/T	
39	Intron 8	2646	G/A		107	Intron 20	1388	C/T	
40	Intron 8	2925	C/G		108	Intron 20	1564	G/A	
41	Intron 8	3222	T/C	rs1965848	109	Intron 20	1873	G/A	
42	Exon 9	4	G/T(Val330Phe)	rs2886059	110	Intron 20	2427	G/C	
43	Exon 10	109	G/T(Leu395Leu)	rs2305230	111	Intron 20	2458	C/T	
44	Intron 10	(671-672)	AG/ins		112	Intron 20	2500	G/C	rs2276726
45	Intron 11	8	C/A	rs2305229	113	Intron 20	2544	C/T	rs2276727
46	Intron 11	447	G/A		114	Intron 20	2573	C/T	rs2276729
47	Intron 11	601	A/G		115	Intron 20	2574	G/A	rs2276730
48	Intron 11	639	G/A		116	Exon 21	31	A/G(Asp793Gly)	rs1127717
49	Exon 12	97	A/G(Ser481Gly)	rs2276724	117	Exon 21	33	G/A(Val794Met)	
50	Intron 12	66	G/del		118	Exon 21	87	A/G(Ile812Val)	
51	Intron 12	478	A/del		119	Intron 21	323	C/G	
52	Intron 12	684	C/T		120	Intron 21	361	C/G	
53	Intron 12	767	A/G		121	Intron 21	478	C/A	
54	Intron 12	1014	C/T		122	Intron 21	1086	C/T	
55	Intron 12	1359	C/T		123	Intron 22	235	A/C	
56	Intron 12	1734	G/T	rs2069033	124	Intron 22	313	G/A	
57	Intron 12	1901	G/A	rs236501	125	Intron 22	1214	G/C	
58	Intron 12	-492	C/T	rs1562474	126	Intron 22	1226	T/C	
59	Intron 12	-470	T/C		127	Intron 22	1623	C/G	
60	Intron 12	-334	T/C		128	Intron 22	1698	A/G	
61	Intron 12	-325	T/C		129	3' Flanking	145	C/T	
62	Intron 12	-221	G/C	rs2305224	130	3' Flanking	239	G/A	
63	Intron 12	-4	T/C	rs2305228	131	3' Flanking	288	C/T	
64	Intron 13	34	T/C		132	3' Flanking	1513	A/C	
65	Intron 13	58	A/G		133	3' Flanking	1707	C/T	
66	Intron 13	125	T/C		134	3' Flanking	1709	C/T	
67	Intron 13	126	G/A		135	3' Flanking	1745	C/T	
68	Intron 13	281	T/G		136	3' Flanking	1843	G/A	

ALDH1L1 (FTHFD), Formyltetrahydrofolate dehydrogenase

Table 7f. Summary of genetic variations detected in the *ALDH2* gene

No.	Location	Position ^a	Genetic variation	NCBI SNP ID
1	5' Flanking	−324	G/A ^{b,c}	rs886205
2	Intron 3	1766	C/del	
3	Intron 6	348	T/C	rs440
4	Intron 6	483	T/C	rs441
5	Intron 8	52	G/C	
6	Intron 8	69	G/A	
7	Intron 9	5197	C/A	
8	Intron 11	114	T/C	
9	Exon 12	104	G/A(Glu503Lys) ^d	rs671
10	3' Flanking	411	T/C	
11	3' Flanking	(432–433)	TC/del	
12	3' Flanking	488	G/T	

ALDH2, Aldehyde dehydrogenase 2 family

^bSNP previously reported by Chou et al. (1999)^cSNP previously reported by Harada et al. (1999)^dSNP previously reported by Yoshida et al. (1985)**Table 7g.** Summary of genetic variations detected in the *ALDH3A1* gene

No.	Location	Position ^a	Genetic variation	NCBI SNP ID
1	5' Flanking	−758	C/A	
2	5' Flanking	−308	C/T	
3	5' Flanking	−294	G/A	
4	5' Flanking	−3	G/A	
5	Intron 1	90	A/C	rs2072327
6	Intron 1	2323	C/T	
7	Intron 1	2499	T/C	
8	Intron 1	2943	A/G	
9	Intron 3	431	C/T	rs887240
10	Exon 4	6	G/T(Ala134Ser)	rs887241
11	Intron 4	235	C/T	rs2072328
12	Intron 5	72	G/C	
13	Intron 5	436	C/G	rs2072329
14	Exon 6	52	T/A(Pro247Pro)	rs2072330
15	Intron 7	633	G/A	
16	Exon 8	36	C/G(Pro329Ala) ^b	rs2228100
17	Intron 9	(40–41)	C/ins	
18	Intron 9	322	G/del	
19	Exon 11	102	C/T(3' UTR)	rs917520
20	Exon 11	228	G/A(3' UTR)	rs1042183

ALDH3A1, Aldehyde dehydrogenase 3 family, member A1

^bSNP previously reported by Tsukamoto et al. (1997)**Table 7h.** Summary of genetic variations detected in the *ALDH3A2* gene

No.	Location	Position ^a	Genetic variation	NCBI SNP ID	No.	Location	Position ^a	Genetic variation	NCBI SNP ID
1	Intron 1	39	C/T		14	Intron 5	254	T/G	
2	Intron 2	634	A/T	rs1004490	15	Intron 6	52	G/C	rs1800869
3	Intron 3	31	T/C	rs1004491	16	Intron 6	137	T/C	
4	Intron 3	2491	T/A		17	Intron 6	923	G/A	
5	Intron 3	2595	T/A		18	Intron 7	331	A/del	
6	Intron 3	2775	G/A		19	Intron 8	643	C/T	
7	Intron 3	3424	G/A	rs2072333	20	Intron 8	666	G/A	
8	Intron 3	3521	A/G	rs962800	21	Intron 9	2129	G/T	
9	Intron 3	3676	G/A	rs2072332	22	Exon 10	1624	G/A(3' UTR)	rs7215
10	Intron 4	481	G/T		23	Exon 10	(1894–1895)	CA/del(3' UTR)	
11	Intron 4	769	G/A		24	3' Flanking	31	T/del	
12	Intron 4	796	A/G		25	3' Flanking	106	G/A	
13	Intron 4	965	A/G	rs1034897	26	3' Flanking	1630	A/G	

ALDH3A2, Aldehyde dehydrogenase 3 family, member A2

Table 7i. Summary of genetic variations detected in the *ALDH3B1* gene

No.	Location	Position ^a	Genetic variation	NCBI SNP ID	No.	Location	Position ^a	Genetic variation	NCBI SNP ID
1	5' Flanking	−1575	G/A	rs308338	21	Intron 7	277	C/T	rs2286165
2	5' Flanking	−1455	C/T		22	Intron 7	498	C/T	
3	5' Flanking	−1352	T/C	rs557098	23	Intron 8	14	C/T	
4	Intron 1	464	A/G		24	Intron 8	49	C/T	
5	Intron 1	2269	G/C		25	Intron 8	111	A/T	
6	Intron 2	1349	C/T		26	Intron 8	2785	T/C	rs105147
7	Intron 2	1820	C/G		27	Intron 8	3219	A/G	rs2286164
8	Intron 2	2046	C/G		28	Exon 9	33	C/T(Ser383Ser)	rs2286163
9	Intron 2	2133	C/T	rs475325	29	Intron 9	946	C/A	
10	Intron 2	2939	G/A		30	Intron 9	1067	C/T	
11	Intron 3	7	C/T		31	Intron 9	1427	C/T	rs308342
12	Intron 4	36	T/C		32	Intron 9	1490	C/T	rs886701
13	Intron 5	40	A/G	rs1636207	33	Exon 10	83	G/A(Pro433Pro)	rs308341
14	Intron 6	(116–117)	CT/del		34	Exon 10	137	G/A(Leu451Leu)	
15	Intron 6	263	T/C	rs2286169	35	Exon 10	397	G/A(3' UTR)	
16	Intron 6	1298	T/G		36	Exon 10	1198	C/T(3' UTR)	
17	Intron 6	1411	C/T		37	Exon 10	1416	T/C(3' UTR)	rs15518
18	Exon 7	185	C/T(Tyr249Tyr)	rs2286168	38	Exon 10	1475	G/A(3' UTR)	
19	Exon 7	339	G/A(Gly301Ser)		39	3' Flanking	15	A/G	
20	Intron 7	249	G/A	rs2286166	40	3' Flanking	60	G/C	

ALDH3B1, Aldehyde dehydrogenase 3 family, member B1

Table 7j. Summary of genetic variations detected in the *ALDH3B2* gene

No.	Location	Position ^a	Genetic variation	NCBI SNP ID	No.	Location	Position ^a	Genetic variation	NCBI SNP ID
1	Intron 1	98	G/A	rs2279123	11	Exon 3	72	T/G(5' UTR)	
2	Intron 1	157	T/C		12	Intron 4	35	A/G	rs1871032
3	Intron 1	354	C/G	rs2279124	13	Intron 5	29	T/C	rs1551887
4	Intron 1	851	T/G		14	Intron 8	375	C/T	
5	Intron 1	894	T/G		15	Intron 8	463	G/A	
6	Intron 1	-463	C/G		16	Exon 9	33	C/A(Ser302Arg)	
7	Exon 2	61	G/A(5' UTR)		17	Intron 9	23	C/T	rs1979376
8	Intron 2	8	A/G		18	Intron 9	95	C/T	rs1979375
9	Intron 2	23	G/C	rs2126716	19	Exon 10	388	G/A(3' UTR)	rs866907
10	Intron 2	(180-181)	A/ins		20	Exon 10	428	C/T(3' UTR)	

ALDH3B2, Aldehyde dehydrogenase 3 family, member B2

Table 7k. Summary of genetic variations detected in the *ALDH5A1* gene

No.	Location	Position ^a	Genetic variation	NCBI SNP ID	No.	Location	Position ^a	Genetic variation	NCBI SNP ID
1	5' Flanking	-1303	G/A		26	Intron 4	2456	T/del	
2	5' Flanking	-301	C/T		27	Intron 4	2501	A/G	
3	5' Flanking	-250	C/G	rs2744575	28	Intron 4	2515	A/G	rs2817225
4	5' Flanking	-221	C/T		29	Intron 4	2548	G/A	rs2328824
5	5' Flanking	-175	C/G		30	Intron 4	-(64-46)	(T) ₁₆₋₁₈	
6	5' Flanking	-174	G/A		31	Intron 4	-27	G/C	
7	Exon 1	106	G/C(Gly36Arg)		32	Intron 5	2783	A/G	rs807513
8	Intron 1	326	G/A		33	Intron 5	3278	T/G	rs807514
9	Intron 1	476	G/A	rs2817213	34	Intron 5	(4621-4624)	CTTA/del	
10	Intron 1	736	G/C	rs2010190	35	Intron 5	(4677-4678)	C/ins	
11	Intron 1	5551	T/G		36	Intron 7	(432-443)	(A) ₁₀₋₁₂	
12	Intron 1	5555	T/del		37	Intron 7	1551	C/T	rs807517
13	Intron 1	5843	C/T	rs2245674	38	Intron 7	3090	C/A	rs807518
14	Intron 1	6061	G/C	rs2245668	39	Intron 7	(3243-3244)	GT/del	
15	Intron 2	306	T/del		40	Intron 7	4987	A/del	
16	Exon 3	100	C/T(His180Tyr)	rs2760118	41	Intron 8	2479	T/C	rs2247845
17	Exon 3	107	C/T(Pro182Leu)		42	Intron 8	2540	G/A	rs2267539
18	Intron 3	201	G/T		43	Intron 8	2717	C/T	
19	Intron 3	237	G/A	rs2817219	44	Intron 9	669	G/A	rs2744597
20	Intron 3	528	C/T	rs2760117	45	Intron 9	1100	G/C	rs2744601
21	Intron 3	577	C/T	rs2760116	46	Exon 10	459	C/A(3' UTR)	rs1054899
22	Intron 3	1369	A/G	rs2744583	47	3' Flanking	916	G/A	rs2744602
23	Exon 4	42	C/T(Ala217Ala)		48	3' Flanking	2711	G/A	
24	Intron 4	2306	T/C		49	3' Flanking	2777	G/A	
25	Intron 4	(2334-2346)	(T) ₁₁₋₁₃						

ALDH5A1, Aldehyde dehydrogenase 5 family, member A1

Table 7l. Summary of genetic variations detected in the *ALDH6A1* gene

No.	Location	Position ^a	Genetic variation	NCBI SNP ID	No.	Location	Position ^a	Genetic variation	NCBI SNP ID
1	5' Flanking	-1303	G/C		17	Intron 2	2333	G/del	
2	5' Flanking	-(1273-1270)	AATT/del		18	Intron 4	138	A/G	
3	5' Flanking	-837	G/A	rs2239556	19	Intron 4	200	T/C	
4	5' Flanking	-831	C/G	rs2239557	20	Intron 5	291	G/A	
5	5' Flanking	-387	G/T	rs2006732	21	Intron 6	13	C/A	rs2072293
6	5' Flanking	-379	A/T	rs2006731	22	Intron 6	174	T/C	rs2072294
7	5' Flanking	-110	G/A	rs2074938	23	Intron 7	209	C/A	
8	Intron 1	142	T/A	rs2074939	24	Intron 8	263	C/G	rs1125606
9	Intron 1	437	A/T		25	Intron 8	287	C/T	
10	Intron 1	835	T/del		26	Intron 9	877	C/T	
11	Intron 1	1294	T/C		27	Intron 9	885	T/G	
12	Intron 1	1447	A/G		28	Intron 11	40	A/C	
13	Intron 1	2536	T/C		29	3' Flanking	33	T/C	rs8204
14	Intron 1	2703	G/T		30	3' Flanking	520	C/T	
15	Intron 1	2802	T/C		31	3' Flanking	1026	T/C	
16	Intron 2	174	T/G	rs765719	32	3' Flanking	1035	G/C	

ALDH6A1, Aldehyde dehydrogenase 6 family, member A1

Table 7m. Summary of genetic variations detected in the *ALDH8A1* gene

No.	Location	Position ^a	Genetic variation	NCBI SNP ID	No.	Location	Position ^a	Genetic variation	NCBI SNP ID
1	5' Flanking	−(837–836)	AT/ins		15	Intron 4	2586	C/A	rs2235262
2	5' Flanking	−702	C/T		16	Intron 4	2861	C/G	rs2235261
3	5' Flanking	−642	G/A		17	Intron 5	311	C/T	rs2072827
4	5' Flanking	−84	G/T		18	Intron 5	356	G/C	rs2072826
5	Intron 1	5437	T/C		19	Intron 5	463	C/T	rs2072825
6	Intron 1	(5836–5855)	(CAAAA) _{4–5}		20	Intron 5	866	C/A	rs2294321
7	Exon 3	146	G/T(Pro144Pro)		21	Intron 5	1719	C/A	rs2294319
8	Intron 4	1033	C/T		22	Intron 6	1146	C/G	
9	Intron 4	1037	C/T		23	Intron 6	1503	A/T	rs2294318
10	Intron 4	1038	A/G	rs1022491	24	Intron 6	1744	C/T	
11	Intron 4	1462	A/C	rs2142725	25	Intron 6	3898	T/G	rs728030
12	Intron 4	1662	G/A		26	Intron 6	9802	A/T	
13	Intron 4	2046	A/C		27	Exon 7	(1089–1098)	(A) _{9–10} (3' UTR)	
14	Intron 4	2394	A/C	rs2235263	28	3' Flanking	848	T/C	

ALDH8A1, Aldehyde dehydrogenase 8 family, member A1

Table 7n. Summary of genetic variations detected in the *ALDH9A1* gene

No.	Location	Position ^a	Genetic variation	NCBI SNP ID	No.	Location	Position ^a	Genetic variation	NCBI SNP ID
1	Exon 1	121	G/A(5' UTR)		16	Intron 3	368	G/del	
2	Intron 1	67	C/G		17	Intron 3	493	A/G	rs1337442
3	Intron 1	103	A/G		18	Intron 3	716	C/G	rs1913844
4	Intron 1	1818	A/del		19	Intron 4	191	T/A	rs2882006
5	Intron 2	5739	T/C	rs1538115	20	Intron 4	557	A/G	
6	Intron 2	5891	G/A		21	Intron 5	830	G/C	
7	Intron 2	6398	T/G		22	Intron 5	838	C/T	
8	Intron 2	9677	A/G		23	Intron 6	120	A/C	
9	Intron 2	9991	C/T		24	Intron 6	2569	T/C	
10	Intron 2	10198	A/G		25	Intron 8	1414	T/C	rs2176151
11	Intron 2	10256	T/del		26	Intron 9	664	T/del	
12	Intron 2	11382	T/C		27	Intron 9	2170	T/del	
13	Intron 2	11455	C/T		28	Exon 11	587	A/del(3' UTR)	
14	Intron 2	12044	C/T		29	Exon 11	712	C/A(3' UTR)	rs12670
15	Intron 3	334	T/del		30	Exon 11	876	T/C(3' UTR)	rs11506

ALDH9A1, Aldehyde dehydrogenase 9 family, member A1

Table 8. Number and regions of SNPs detected in 14 *ALDH* genes

Gene	5' Flanking	Intron	3' Flanking	Exon				Total
				5' UTR	Coding		3' UTR	
					Nonsynonymous	Synonymous		
<i>ALDH1A1</i>	1	33	5	0	0	1	0	40
<i>ALDH1A2</i>	1	98	8	0	1	0	0	108
<i>ALDH1A3</i>	4	53	5	0	1	0	6	69
<i>ALDH1B1</i>	0	5	1	0	3	1	1	11
<i>ALDH1L1</i>	0	113	8	0	6	1	0	128
<i>ALDH2</i>	1	6	2	0	1	0	0	10
<i>ALDH3A1</i>	4	9	0	0	2	1	2	18
<i>ALDH3A2</i>	0	20	2	0	0	0	1	23
<i>ALDH3B1</i>	3	25	2	0	1	4	4	39
<i>ALDH3B2</i>	0	14	0	2	1	0	2	19
<i>ALDH5A1</i>	6	25	3	0	3	1	1	39
<i>ALDH6A1</i>	6	19	4	0	0	0	0	29
<i>ALDH8A1</i>	3	20	1	0	0	1	0	25
<i>ALDH9A1</i>	0	20	0	1	0	0	2	23
Total	29	460	41	3	19	10	19	581

SNP, Single-nucleotide polymorphism; UTR, untranslated region

Table 9. Novel SNPs detected in exons of 14 *ALDH* genes

Region	Gene	Location	Position	SNP
5' UTR	<i>ALDH3B2</i>	Exon 2	61	G/A
		Exon 3	72	T/G
	<i>ALDH9A1</i>	Exon 1	121	G/A
Coding Nonsynonymous	<i>ALDH1A2</i>	Exon 9	141	G/A(Val348Ile)
	<i>ALDH1A3</i>	Exon 10	88	A/G(Met386Val)
	<i>ALDH1B1</i>	Exon 2	614	C/T(Thr202Ile)
	<i>ALDH1L1</i>	Exon 7	41	T/C(Leu254Pro)
		Exon 21	33	G/A(Val794Met)
	<i>ALDH3B1</i>	Exon 21	87	A/G(Ile812Val)
		Exon 7	339	G/A(Gly301Ser)
	<i>ALDH3B2</i>	Exon 9	33	C/A(Ser302Arg)
	<i>ALDH5A1</i>	Exon 1	106	G/C(Gly36Arg)
		Exon 3	107	C/T(Pro182Leu)
	<i>ALDH3B1</i>	Exon 10	137	G/A(Leu451Leu)
	<i>ALDH5A1</i>	Exon 4	42	C/T(Ala217Ala)
	<i>ALDH8A1</i>	Exon 3	146	G/T(Pro144Pro)
	<i>ALDH1A3</i>	Exon 13	104	G/C
		Exon 13	281	C/T
	<i>ALDH3B1</i>	Exon 10	397	G/A
		Exon 10	1198	C/T
3' UTR	<i>ALDH3B2</i>	Exon 10	1475	G/A
		Exon 10	428	C/T

SNP, Single-nucleotide polymorphism; UTR, untranslated region

Laurenzi et al. 1996; Lin et al. 1996) were not found in our examination of a Japanese test population. However, we did identify ten novel nonsynonymous polymorphisms in other *ALDH* genes. The polymorphisms published here should be useful for investigating relationships between individual genotypes and susceptibility to certain diseases and/or the potential efficacy or adverse effects of certain drugs.

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