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Catalog of 258 single-nucleotide polymorphisms (SNPs) in genes encoding three organic anion transporters, three organic anion-transporting polypeptides, and three NADH:ubiquinone oxidoreductase flavoproteins

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Abstract We present here a series of high-density maps of single-nucleotide polymorphisms (SNPs) detected in genes encoding three organic-anion transporters, three organic anion-transporting polypeptides, and three nicotinamide adenine dinucleotide, reduced:ubiquinone oxidoreductase flavoproteins. A total of 258 SNPs were identified among these nine genes through systematic screening of DNA from 48 Japanese individuals: 17 in 5′ flanking regions, three in 5′ untranslated regions, 13 in coding regions, 211 in introns, six in 3′ untranslated regions, and 8 in 3′ flanking regions. By comparing our data with SNPs deposited in the dbSNP database in the National Center for Biotechnology Information, we determined that 236 (91.5%) were novel. In addition, 46 genetic variations of other types were discovered within these loci. These high-resolution maps will serve as a useful resource for analyzing potential associations between variations in these nine genes and differences in human susceptibilities to common diseases or response to drug therapies.

Key words Single-nucleotide polymorphisms (SNPs) · High-density SNP map · Nonsynonymous substitutions · Insertion–deletion polymorphism · Japanese population · Human organic-anion transporter genes · Human organic anion-transporting polypeptide genes · NADH:ubiquinone oxidoreductase flavoprotein genes

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Introduction

A major goal of the Human Genome Project is to understand the role of common genetic variations as regards susceptibility to common diseases and differences among individuals with respect to therapeutic efficacy and/or side effects of drugs. To achieve this aim, we established two different screening systems to explore single-nucleotide polymorphisms (SNPs) across the human genome. One approach was intended to identify up to 150,000 SNPs within transcription units in the Japanese population; more than 130,000 SNPs have been discovered already and that information (as of the middle of June 2001) is available from our worldwide website (http://snp.ims.u-tokyo.ac.jp/). Second, we focused on variations in genomic regions that correspond to genes encoding drug-metabolizing enzymes and transporters. Approximately 1300 SNPs and other variations within such loci have been reported (Iida et al. 2001a,b,c,d; Saito et al. 2001a,b; Sekine et al. 2001). Moreover, we established a high-throughput system for genotyping up to 100 million SNPs per year, using a multiplex polymerase chain reaction (PCR) method with the Invader assay (Ohnishi et al. 2001). The identification of SNPs at specific loci, coupled with our high-throughput genotyping system, should allow investigators to resolve complex diseases or predict drug responses within a few years.

Organic-anion transporters (OATs) are membrane proteins with 12 putative membrane-spanning domains; these molecules function as sodium-independent exchangers or facilitators, handling a wide variety of clinically important compounds (antibiotics, nonsteriodal anti-inflammatory drugs [NSAIDs]) and toxins (see reviews by Sekine et al. 2000; Sweet et al. 2001). So far, four mammalian OAT isoforms (OAT1, OAT2, OAT3, and OAT4) and one fish isoform (fROAT) have been identified (Sekine et al. 2000). Among them, OAT1 is a *p*-aminohippurate (PAH)/dicarboxylate exchanger that mediates the high-affinity transport of PAH in a sodium-independent manner. Human OAT1 (hOAT1) and rat OAT1 (rOAT1) are able

to transport anionic drugs including cephaloridine (a β-lactam antibiotic); NSAIDs such as aspirin, indomethacin, and salicylate; methotrexate (an antitumor drug); and penicillin G, as well as various endogenous substrates like organic anions, prostaglandin E2 (PGE2), glutarate, α-ketoglutarate, cyclic adenosine monophosphate, and cyclic guanosine monophosphate. OAT3, for its part, mediates transport of dehydroepiandrosterone sulfate, ochratoxin A, PGE2, estradiol glucuronide, and glutarate. With a substrate spectrum as diverse as that of OAT1, OAT3 also interacts with anionic metabolites of neurotransmitters such as adrenaline, noradrenaline, and serotonin. Human OAT3 (hOAT3) is located in the basolateral membrane of renal proximal tubules (Cha et al. 2001), where it interacts with chemically heterogeneous anionic compounds including NSAIDs, diuretics, sulfobromophthalein, penicillin G, bile salts, and tetraethyl ammonium bromide. *hOAT2* was isolated from a human kidney cDNA library as the counterpart of rat *OAT2* (Kok et al. 2000), but its functional properties are not clear.

Organic anion-transporting polypeptide (Oatp1) was first identified in rats as a multispecific and sodium ion-independent transporter for various organic anions including bile acids, conjugated metabolites, and xenobiotics (Jacquemin et al. 1994). Human OATP1 (hOATP1; originally referred to as OATP), an ortholog of rat Oatp1, is localized mainly in brain and liver; it mediates hepatocellular uptake of organic anions including bile acids, sulfobromosulphophthalein (BSP), estrone-3-sulfate, estradiol-17-glucuronide ($E_2$17βG), the cardiac glycoside ouabain, and even the cationic compound N-(4,4-azo-n-pentyl)-21-deoxy-ajmalinium (Kullak-Ublick et al. 1995; Bossuyt et al. 1996). Human OATP2 (hOAT2) is also expressed specifically in liver, where it is localized at the basolateral membrane of hepatic parenchymal cells; it plays a crucial role in the sinusoidal uptake of anionic drugs and metabolites (Abe et al. 1999; Hsiang et al. 1999; Konig et al. 2000a; Tamai et al. 2000). Human OATP8 (hOAT8) can transport several typical organic anions, e.g., BSP, $E_2$17βG, and dehydroepiandrosterone sulfate, but not bile salts (Konig et al. 2000b). So far, five genes encoding organic anion-transporting polypeptides have been identified in humans (Konig et al. 2000b).

Nicotinamide adenine dinucleotide, reduced (NADH):ubiquinone oxidoreductase (complex I) removes electrons from NADH and passes them on to the electron acceptor ubiquinone. This is the first step in the transfer of electrons, through a number of intermediates, to oxygen, and drives the production of adenosine triphosphate (Walker 1992). Complex I, a complex of integral membrane proteins, is composed of more than 42 subunits, 7 of which are encoded by the mitochondrial genome and the remainder by the nuclear genome (Smeitink and van den Heuvel 1999). Complex I consists of (1) a flavoprotein fraction, containing binding sites for NADH, flavin mononucleotide, and iron–sulfur (Fe–S) clusters; (2) an iron–protein fraction with several Fe–S clusters; and (3) a hydrophobic fraction, which binds quinone, in the inner membrane. The flavoprotein fraction is composed of a 51-kDa subunit (NDUFV1), a 24-kDa subunit (NDUFV2), and a 10-kDa subunit (NDUFV3), all encoded by the nuclear genome (Ali et al. 1993; de Coo et al. 1995, 1997, 1999). This fraction may play a catalytic role in the oxidation of NADH, as it is associated with flavoproteins and NAD binding. Mutation in *NDUFV1, NDUFS1, NDUFS4, NDUFS7, or NDUFS8* results in mitochondrial complex I deficiency (OMIM #252010; Benit et al. 2001). Earlier we constructed high-density SNP maps of 18 Complex-I gene loci, in which a total of 241 SNPs were identified (Iida et al. 2001b).

In the present report, we provide a series of fine-scale maps of variations within three organic anion-transporter genes, three organic anion-transporting polypeptide genes, and three NADH:ubiquinone oxidoreductase flavoprotein genes. These maps contain a total of 258 SNPs and 46 variations of other types detected in a Japanese population sample.

Subjects and methods

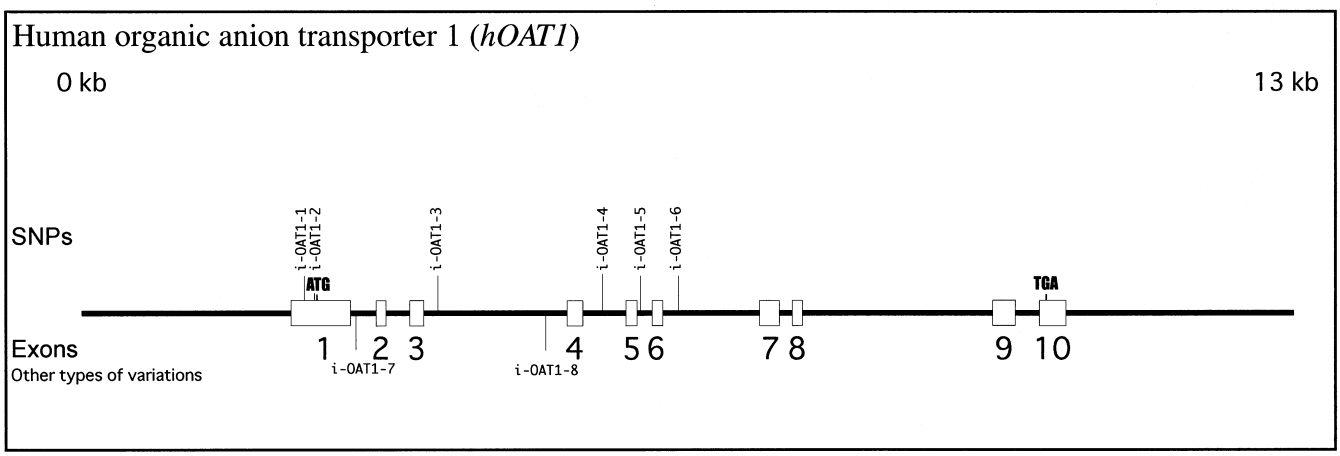
Blood samples were obtained with written informed consent from 48 healthy Japanese volunteers for this study, which was approved by the ethical committee of the RIKEN SNP Research Center. On the basis of genomic sequences from the GenBank database, we designed primers to amplify each gene in its entirety, as well as 2 kb upstream of the first exon and downstream of the last exon. However, we excluded from the screening protocol most of the regions corresponding to repetitive sequences predicted by the RepeatMasker program. DNA extraction, PCR experiments, and DNA sequencing were performed according to methods described on our worldwide website (http://snp.ims.u-tokyo.ac.jp/). Each PCR was carried out using 20 ng of DNA pooled from three individuals. All SNPs detected by the PolyPhred computer program (Nickerson et al. 1997) were confirmed by sequencing both strands of each PCR product.

Genbank accession numbers for *OAT*, *OATP*, and *NDUFV* genomic sequences:

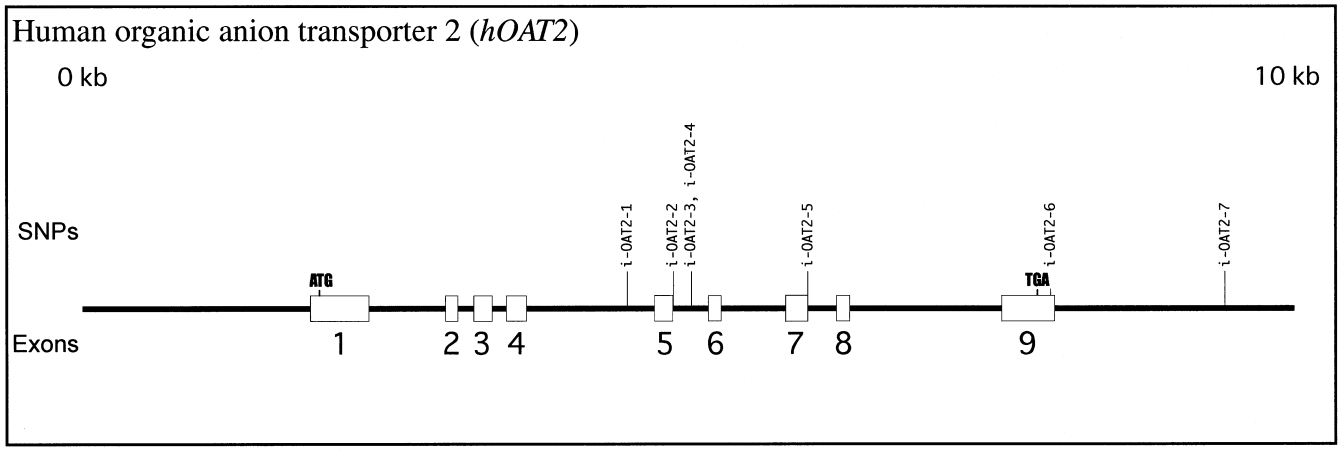
hOAT1: AP001858.3, AJ249369.1, and AP000438.4
hOAT2: AC26532.3
hOAT3: AP001858.3
hOATP1: AC022224.22
hOATP2: NT_024399.2
hOATP8: NT_024399.2
NDUFV1: NT_009304.2
NDUFV2: NT_011024.2
NDUFV3: AP001748.1

Results and discussion

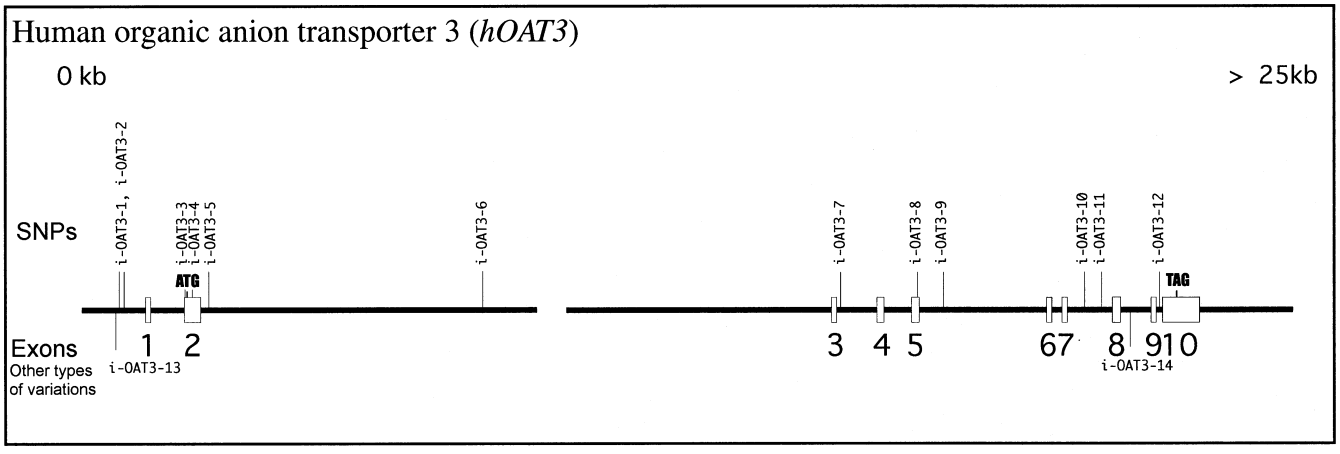
We present here a series of high-density SNP maps that include a total of 258 SNPs present in a Japanese population sample among nine genes (three *hOATs*, three *hOATPs*, and three *NDUFVs*) that are involved in the metabolism of



a

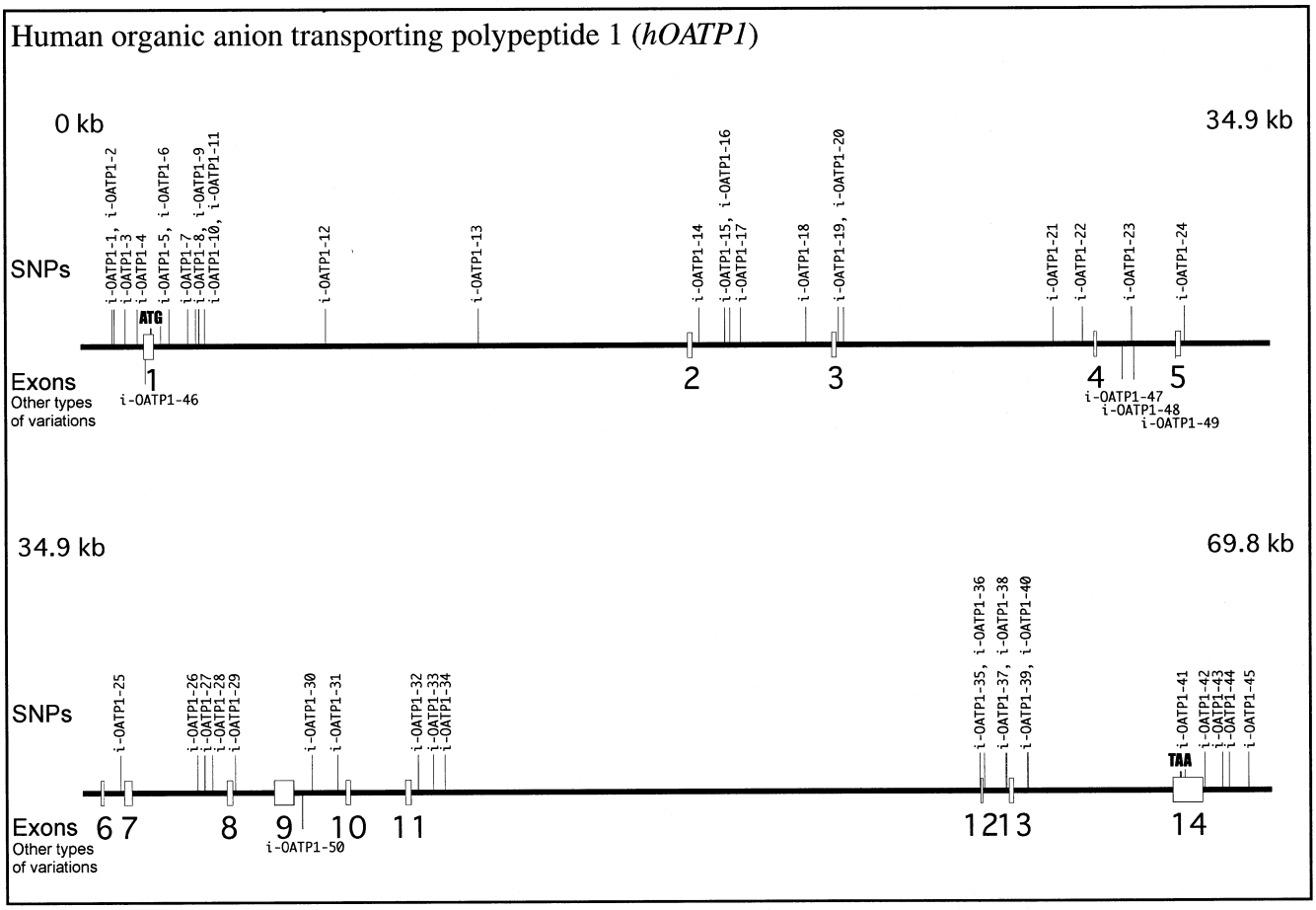


b



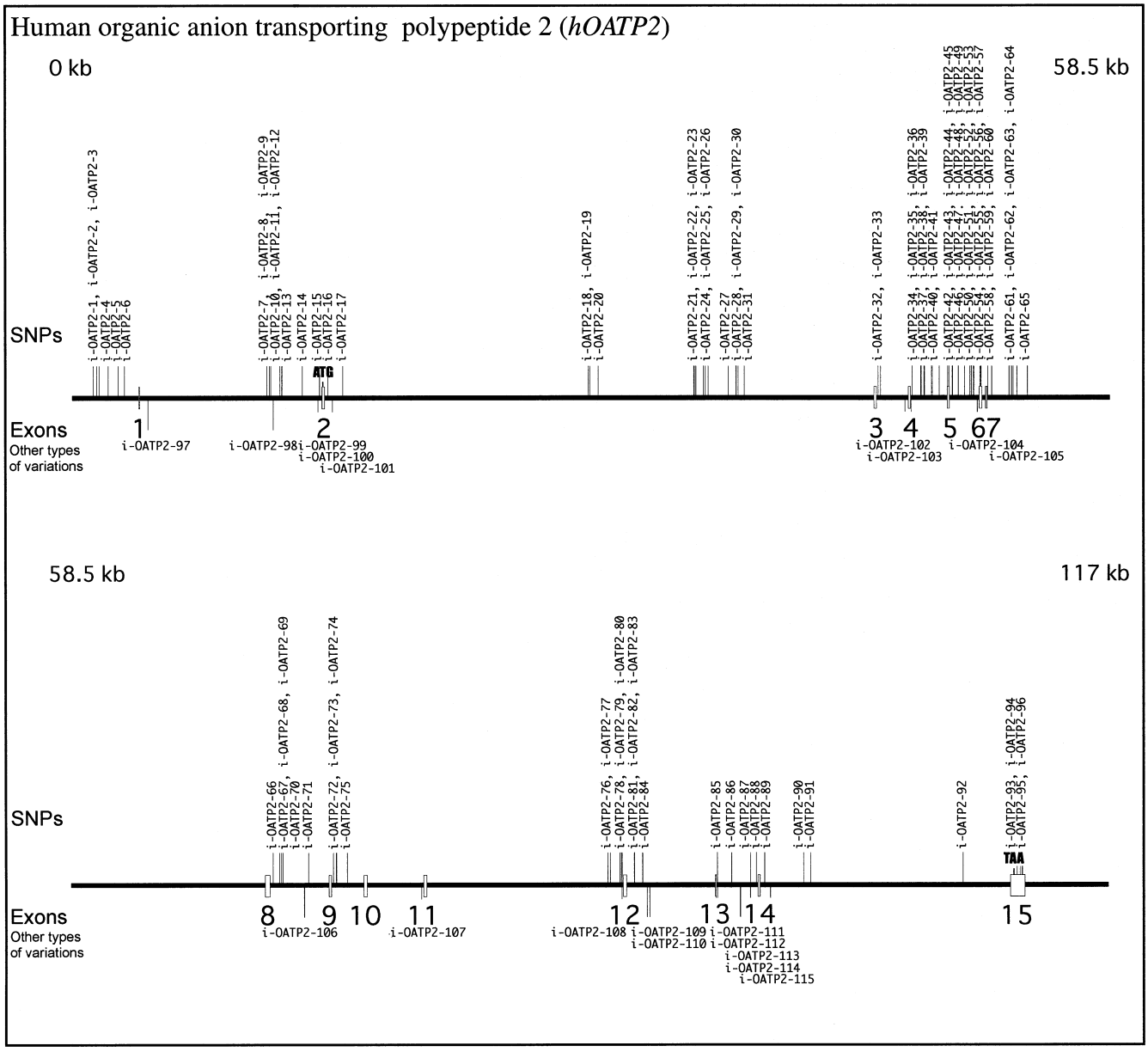
c

Fig. 1a–i. Genomic organizations and locations of single-nucleotide polymorphisms (*SNPs*) in nine genes encoding three organic-anion transporters (**a–c**), three organic anion-transporting polypeptides (**d–f**), and three NADH:ubiquinone oxidoreductase flavoproteins (**g–i**). Detailed information about each variation is given in Table 1. Exons and introns are represented by *rectangles* and *horizontal lines*, respectively. SNPs are indicated *above* the genes (designations correspond to the left-most column on Table 1). Other types of variations, where present, are indicated *below* the genes



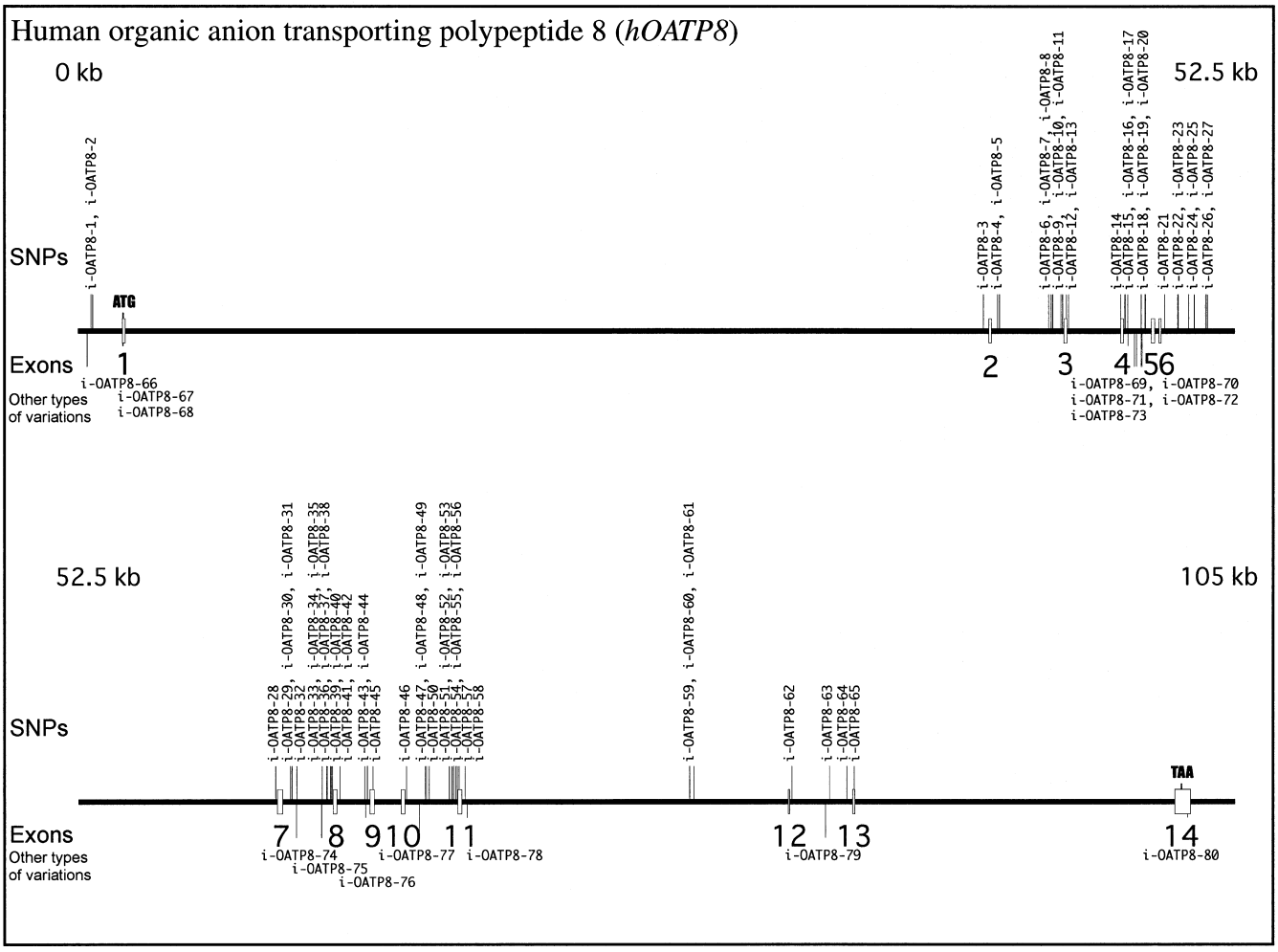
d

Fig. 1a–i. Continued



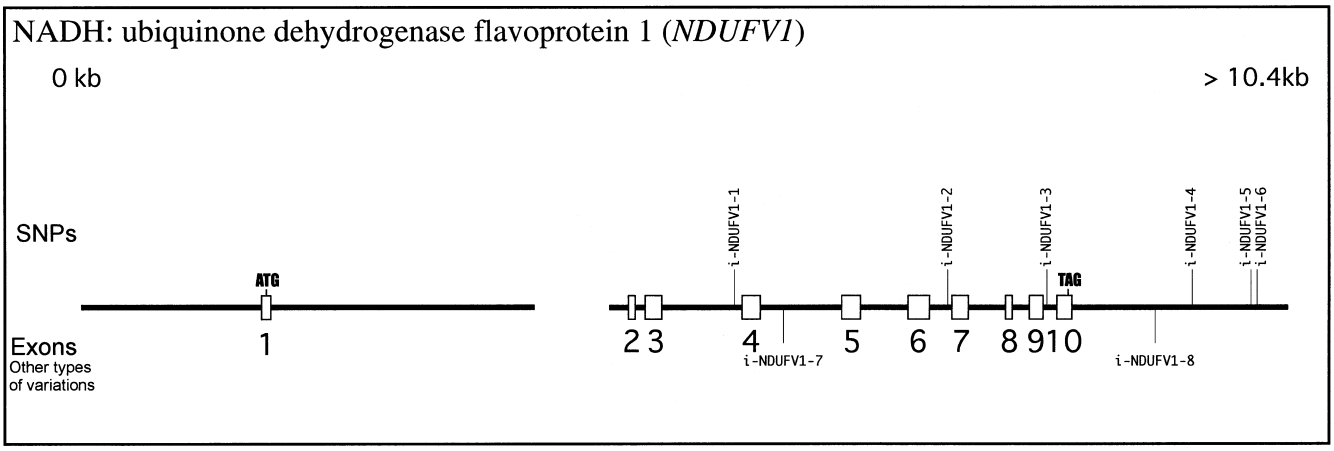
e

Fig. 1a–i. Continued

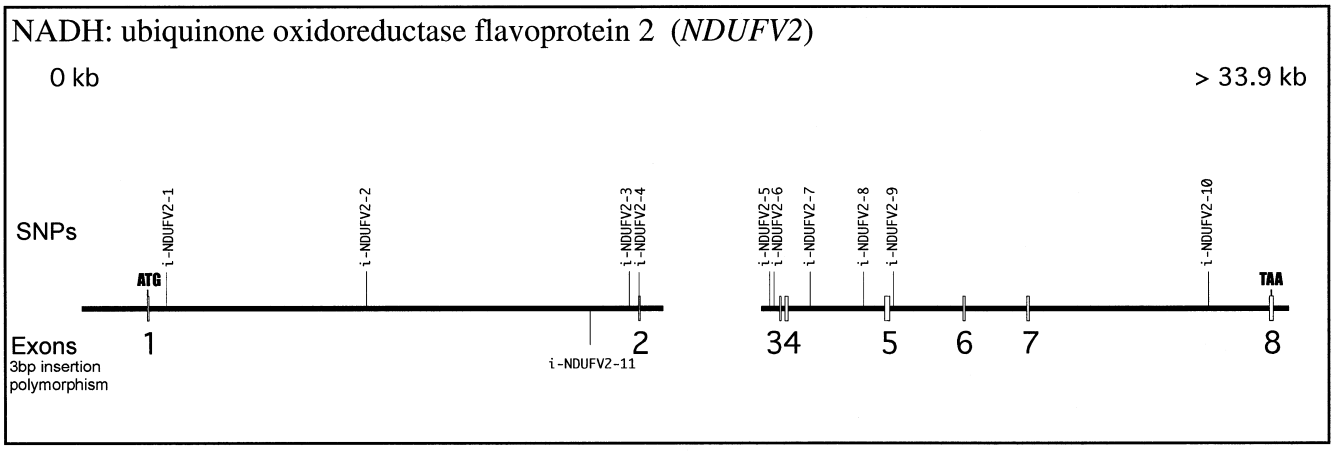


f

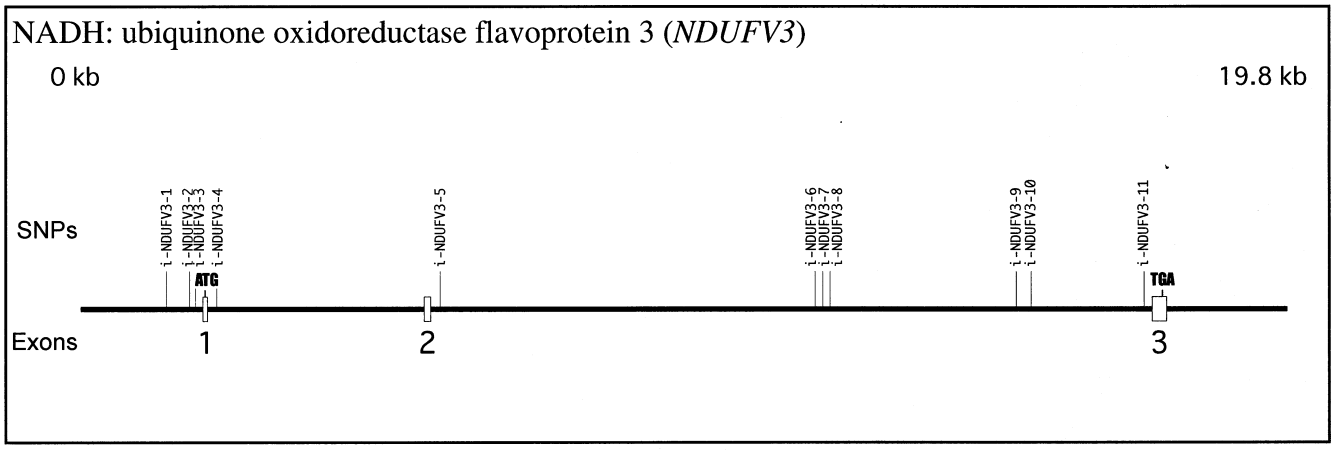
Fig. 1a–i. Continued



g



h



i

Fig. 1a–i. Continued

Table 1. Characterization of variations in the three OAT, three OATP, and three NUDFV gene loci

ID	Region	Position[a]	Flanking sequence[b]	Variation (5' to 3')[c]	Flanking sequence[b]	Substitution	Repetitive sequence[d]	Identity to dbSNP
organic anion transporter 1 (*OAT1*)								
i-OAT1-1	5' untranslated region	-127	gcagctcggactcagctccc	G/A	gagcaacccagctgcggagg			
i-OAT1-2	5' untranslated region	-20	gaaggcctcagcccccagcc	A/G	ctgggctgggcctggcccaa			
i-OAT1-3	intron 3	150	caatagaacaacctttctc	G/A	ggctcatgccgccctgaccc			
i-OAT1-4	intron 4	211	ttctctggcttcccccactc	A/C	gttctccagcctgcctgctc			
i-OAT1-5	intron 5	33	gagacttcccatgataacct	C/T	ccagggcttcacccccaaac			
i-OAT1-6	intron 6	168	gaaccagatgcccccagcct	C/T	gactcagtcccagtctccac			
i-OAT1-7	intron 1	58-71	ggaagatgggggcctttgtt	$(A)_{13-15}$	gtacatggagaaattaactg			
i-OAT1-8	intron 3	1306-1319	aataggttgaggaggagcag	$(A)_{12-15}$	tcaagagtgtggagggggca			
organic anion transporter 2 (*OAT2*)								
i-OAT2-1	intron 4	842	ttgacctccaaaagtgtttg	G/A	attacaggcatgggccattg		+	
i-OAT2-2	intron 5	33	gtgtgtgtgagcatgcatat	C/A	tgtgtgtggtggggagtggg			dbSNP ID:rs1574430
i-OAT2-3	intron 5	183	ccacatccatcattcgagac	A/C	A/Cactcgtctcagctgccatg			
i-OAT2-4	intron 5	184	cacatccatcattcgagacA/C	A/C	actcgtctcagctgccatga			
i-OAT2-5	exon 7	1269	actagactgctagtgtcctc	C/T	ggtgagcccagtcccatagg	Ser423Ser		
i-OAT2-6	3' untranslated region	1792	ataaatgtgtacatgagtgt	A/G	tgaacacaaatacataaggt			
i-OAT2-7	3' flanking region	1386	tgtagcagcccacatcgcca	G/A	tgttcacacctgagagagag			
organic anion transporter 3 (*OAT3*)								
i-OAT3-1	5' flanking region	-580	ctgtgtcagagacacagaca	C/G	ggaggtcctggctgccccag			dbSNP ID:rs948980
i-OAT3-2	5' flanking region	-463	ttcctgagaggcaaatcccc	T/C	tcccctactcgggaggtgcc			
i-OAT3-3	5' untranslated region	-16	cctgcccacagctctggctc	G/A	tcttgccccagtgccatgac			
i-OAT3-4	exon 2	153	cctgtccaccactgtcgccc	G/A	ccccacaatgcctccacagg	Pro51Pro		
i-OAT3-5	intron 2	177	gcaccaagacccttggcttc	T/C	tcccactcagagtccaagca			
i-OAT3-6	intron 2	6201	gctcatcctctctggtcctt	T/G	tgccccagcacaggttcctc			
i-OAT3-7	intron 3	79	tctgctccacccgtgcaccc	G/C	caaagaggcaaagagctggg			
i-OAT3-8	exon 5	723	tggcgttggctgcagttaac	T/A	gtgtccattcccttcttcgt	Thr241Thr		
i-OAT3-9	intron 5	524	tcgaagtacaaaggaaagtt	T/C	aaagagaagcctgagcctgg			
i-OAT3-10	intron 7	386	gaccaatgggtttcagactc	G/A	aagacaaaaattatgtttat			
i-OAT3-11	intron 7	754	gcccacgtcagacatgacca	G/A	tcaatcacagcactttctcc			dbSNP ID:rs953894
i-OAT3-12	intron 9	81	attgtcctgtcctctaccca	G/A	gggagccatcctttatgaac			
i-OAT3-13	5' flanking region	-661 to -660	tacatttggtccccaggggg	G/ins	agcggctgatcaggagagaa			
i-OAT3-14	intron 8	211-212	tctgacttggactgggcaaa	AA/del	gtatggtggtatctggatag			
organic anion transporter peptide 1 (*OATP1*)								
i-OATP1-1	5' flanking region	-916	acagagtagatgttcaataa	G/A	tatttgttgtatctgtgaga		+	
i-OATP1-2	5' flanking region	-843	tagtgcagcgactatgcctt	G/A	atgtgtgtgtgtttgggatt			
i-OATP1-3	5' flanking region	-526	aaatgtgtgcctgtatgtta	T/C	acatctgtacatatatttcc			
i-OATP1-4	5' flanking region	-172	acaaacacaactcaaagtat	G/A	tgtgttattaaaagtagcta			
i-OATP1-5	intron 1	206	ttgattcaggcaagttagtc	C/G	taaatggctttgagagactt			
i-OATP1-6	intron 1	454	caacataacaataatttcct	G/A	taagaaaaatggccattttg			
i-OATP1-7	intron 1	999	gtttagcaaggttagatatt	A/G	atgtggatgttaagacaaaa			
i-OATP1-8	intron 1	1223	ttgctagaagctagtaggac	C/T	agctttataaatacagagat			
i-OATP1-9	intron 1	1326	aactagttaggcaacccatg	T/C	gttttagggG/Aaaaagcaatg			
i-OATP1-10	intron 1	1336	gcaacccatgT/Cgttttaggg	G/A	aaaagcaatgaggtcatgat			

Table 1. Continued

ID	Region	Position[a]	Flanking sequence[b]	Variation (5' to 3')[c]	Flanking sequence[b]	Substitution	Repetitive sequence[d]	Identity to dbSNP
i-OATP1-11	intron 1	1498	atagtttgctcttaagaata	C/T	actctgagaaggtttatagt			
i-OATP1-12	intron 1	5041	ttatgctcccgaggagttag	C/T	tctctaaatgcataaggaga			
i-OATP1-13	intron 1	9532	aaagactgggagcacttccc	A/G	atgacaaatactagactaga			
i-OATP1-14	intron 2	198	ttacctcatattaacaccta	A/C	atattgccacatatcctacc			dbSNP ID:rs2219793
i-OATP1-15	intron 2	961	aaaaagttatatagaaatat	A/G	agtgtcactcctttctagtt			
i-OATP1-16	intron 2	1110	gtctactagtgttcaactcc	T/C	ttagatcttagcctgtatca			
i-OATP1-17	intron 2	1419	aaagcctaagaaggatgcag	T/C	gcaatagcctatgtgagaag			
i-OATP1-18	intron 2	3339	tatggtttgcaaaaaactta	T/C	tcgtatatttgtttttttca			
i-OATP1-19	intron 3	66	caggaaatgaagttgcactt	T/C	cctctctaggagcaatgctt			
i-OATP1-20	intron 3	205	tcagttttgtcaatttacac	A/G	atggggatttgggacctttt			
i-OATP1-21	intron 3	6377	aatgaatagactttgagtta	C/T	tggatttttagtggataaat			
i-OATP1-22	intron 3	7238	tgaatgtcacattttttaaa	G/A	tttgtgttccttatctcata			
i-OATP1-23	intron 4	1016	ttttattctggattcatgtt	T/C	gtggaaattgcagtagtcca			
i-OATP1-24	intron 5	110	tccacaatgatgagtagagt	A/G	tcttggcacagttggccttc		+	
i-OATP1-25	intron 6	496	agtgtctgaattataagcca	A/G	ttttatagttggttgggacc			
i-OATP1-26	intron 7	1934	aaagtgaaaggaaattaaaa	G/C	tgagaacttgagcctgaatg			
i-OATP1-27	intron 7	2140	tagaatgtaccaaatgaatc	A/G	gcatctctgaggatgggacc		+	
i-OATP1-28	intron 7	2365	tgaaatcttctttatcaact	C/T	gattttcctccagactttac			
i-OATP1-29	intron 8	88	gcaaactcctaagttgaagt	G/C	ttttaggatatttttgact			
i-OATP1-30	intron 9	534	tcatattttgtattttaaag	G/A	ttatctgggttttactgaaa			
i-OATP1-31	intron 9	1286	tattcttctgagataaatca	T/C	tgaaggagtggctatgtggt			
i-OATP1-32	intron 11	215	ttcactcctattcctcgcta	C/T	ttttcttccttatttcttag			
i-OATP1-33	intron 11	663	ttcttcttcttttggagctc	T/A	aaagtagagttcagttaatc			
i-OATP1-34	intron 11	999	atcatcactgcatgagagtt	A/G	gaattatctaactttgtgat			
i-OATP1-35	intron 11	16727	tttcttttatttacaaactt	A/G	tttacttttcaggtgtatga			
i-OATP1-36	intron 12	48	ctatcagaacaatattatta	T/G	tattatttttattacactt			
i-OATP1-37	intron 12	686	tatgttttgataaactttgc	C/A	gtacaaataaagaaaattga			
i-OATP1-38	intron 12	708	tacaaataaagaaaattgaa	A/G	tatttccaaataaatcaagt			
i-OATP1-39	intron 13	418	tctctggtctccaaaatcat	A/G	tattttctccctctttaC/Aat			
i-OATP1-40	intron 13	436	atA/Gtattttctccctcttta	C/A	attttgctgaaacaatcttc			
i-OATP1-41	3' untranslated region	2130	gtctttaagaacctaaaaaa	C/A	ctcttaactcaaaataataa			
i-OATP1-42	3' flanking region	57	agtgactaaagtttttctta	C/A	aaacaagtgtctgaatcaaa			
i-OATP1-43	3' flanking region	572	aatacactatggttatttat	G/A	tgtactataaatggagtgag			
i-OATP1-44	3' flanking region	788	atttcctaaatgatcagatg	C/T	atcatatgaaaaaagaaagc			
i-OATP1-45	3' flanking region	1356	aggtgactgacataaatggg	G/A	gcagaggacataatgaggtt			
i-OATP1-46	5' untranslated region	-189 to -188	attttctaatctgtattaaa	A/ins	gcgttccaggtatttttgta			
i-OATP1-47	intron 4	725-726	tgatctttaatagcggggaa	AA/del	caggcaagtacgctatagtt			
i-OATP1-48	intron 4	1082-1083	attgagtcaggaaaccaaaa	CA/del	gtttcaaaaatttgaaaaat			
i-OATP1-49	intron 4	2301	aatgtcatgtctttttttt	T/del	aatgcagagtgtacaaagga			
i-OATP1-50	intron 9	241-246	attgtatgtgcatgtgggtg	TGTGTG/del	catgattgtctttgtgatat			
organic anion transporter peptide 2 (*OATP2*)								
i-OATP2-1	5' flanking region	-2574	ggataaggcaacccctatgt	A/G	tcactgctgcaggagaggga			
i-OATP2-2	5' flanking region	-2366	aacataggaatgtgcagagc	C/T	ctgtggggattagagaagag			dbSNP ID:rs852550
i-OATP2-3	5' flanking region	-2244	tgatgatgccagagctttga	T/G	cattggtgggtatagaaaca			dbSNP ID:rs852549
i-OATP2-4	5' flanking region	-1723	tctttcagacttcaaaggcc	A/G	tgatatttcatcagagctgt			
i-OATP2-5	5' flanking region	-1180	tgcttatttaacaggcataa	T/G	ctttggtctcctgagccaga			
i-OATP2-6	5' flanking region	-811	tatgtgcatatgtgtataca	G/A	gtaaaagtgtgtatatatgt		+	
i-OATP2-7	intron 1	7188	aatcatttgaaatttaagaa	A/G	aaaatatgttcagagaaaaa			

Table 1. Continued

ID	Region	Position[a]	Flanking sequence[b]	Variation (5' to 3')[c]	Flanking sequence[b]	Substitution	Repetitive sequence[d]	Identity to dbSNP
i-OATP2-8	intron 1	7331	gtgaaatgaggaacaaagtg	T/C	ccacctttttttcctgaata			
i-OATP2-9	intron 1	7391	agagagatgtgaaatagtat	T/G	tttctggggaagtaggggaa			
i-OATP2-10	intron 1	7886	ttgttagtagaaagaaaatc	G/A	aagcctaaaactaaaggaag			
i-OATP2-11	intron 1	7958	ttgctattatataatttttt	T/A	A/Taaaaaagatttcctaatat			
i-OATP2-12	intron 1	7959	tgctattatataattttttT/A	A/T	aaaaaagatttcctaatatt			
i-OATP2-13	intron 1	8036	ggaaaaaatggggtgaaatt	A/T	atcaaagggcagcttattac			
i-OATP2-14	intron 1	9164	acattatattctatataaaa	G/T	agtcagttgaagtaaaaagt			
i-OATP2-15	intron 1	10123	tctgtctttcctacttttgt	T/G	tccagcattgacctagcaga		+	dbSNP ID:rs2010668
i-OATP2-16	intron 2	193	tgattaagtatttctttggc	G/A	aaatttttgatgcttaatag			
i-OATP2-17	intron 2	1020	ttgagtaacatttaggccaa	G/A	tggcagtcataaggaaaaag			
i-OATP2-18	intron 2	14865	agaggaattaatcataagag	G/T	tttatttggctaaagtgaca			
i-OATP2-19	intron 2	14931	gttagttaataacagaaaaa	A/T	tatcagaaattttaaaaaat			
i-OATP2-20	intron 2	15417	ttctaaaataagtaagctaa	A/T	tattctatattatactacta			
i-OATP2-21	intron 2	20823	ttgtataagagatacaaaac	A/C	aattcctactaggggaaata			
i-OATP2-22	intron 2	20852	ctaggggaaataaagcttca	G/C	taaggaggtggcattaagct			
i-OATP2-23	intron 2	20930	atggagagaagcagcagtgt	A/G	ccacagataaatgaagtgag			dbSNP ID:rs976754
i-OATP2-24	intron 2	21360	ttcaaaagctgtatttctca	T/C	tagtgctttttgtgaataaa			
i-OATP2-25	intron 2	21467	tatatacacaatacctgtcc	A/G	gaagatgtggtataagccaa			
i-OATP2-26	intron 2	21621	tatcaatacttatgaagaga	A/G	ctaactattctaactaggga			
i-OATP2-27	intron 2	22760	ttccccacctcctgttggtt	C/G	tcctcttaaacttctccttg			
i-OATP2-28	intron 2	23199	cctatctgcacataacatta	C/T	aaacttatggcaattataA/Ga			
i-OATP2-29	intron 2	23218	aC/Taaacttatggcaattata	A/G	aactcaatacatattatact			
i-OATP2-30	intron 2	23330	gcccttgttcctgttcctct	G/A	tacctgcctcaactacatag			
i-OATP2-31	intron 2	23673	ctggagacggtagctcaaac	T/C	gaggatgaaaatagacattt			
i-OATP2-32	intron 3	89	ggttatcaactggggtaaat	T/G	tatctctcacaggcaatttg		+	
i-OATP2-33	intron 3	224	tgctaaatattctataatgc	A/G	caaagaatgatgtaactgaa		+	
i-OATP2-34	intron 4	97	ccctttaaataggcagttac	C/A	ttttgagaagatacccacta			
i-OATP2-35	intron 4	568	ttcatgatccaaattgtggc	A/G	acgtatttccaggcaacaag			
i-OATP2-36	intron 4	599	aggcaacaagatagaagaag	A/G	aaagaataagaagcaacaaa			
i-OATP2-37	intron 4	753	aaaatagacattattccaag	T/A	taccaagttcccggttaaaa			
i-OATP2-38	intron 4	781	ttcccggttaaaaatcccaa	G/C	tataattactgtggaaggaa			
i-OATP2-39	intron 4	1196	aaggaccacaatctagatca	G/T	cattgctctaaatatgccat			
i-OATP2-40	intron 4	1229	tatgccataatatgtgacac	T/C	tttgcacctggtatttctac			
i-OATP2-41	intron 4	1623	catctagttgaaatggatta	G/C	attttattttactacattt			
i-OATP2-42	exon 5	388	attctaaagaaactaatatc	A/G	attcatcagaaaattcaaca	Asn130Asp		
i-OATP2-43	exon 5	452	taatcaaattttatcactca	A/G	tagagcatcacctgagatag	Asn151Ser		
i-OATP2-44	intron 5	165	ttaatatacacagttcgccc	A/T	ttaacaacacaggtttaaac			
i-OATP2-45	intron 5	189	acaacacaggtttaaactac	G/A	cG/Attttcacttctatgcaaa			
i-OATP2-46	intron 5	191	aacacaggtttaaactacG/Ac	G/A	ttttcacttctatgcaaatt			
i-OATP2-47	intron 5	507	atataactttgctttcattg	C/T	aaaaggcaaactG/Attatatc			
i-OATP2-48	intron 5	520	ttcattgC/Taaaaggcaaact	A/G	ttatatcatttaaagacttt			
i-OATP2-49	intron 5	856	agtcatgataaacctaatag	A/G	ataaaacaacaaaaaagaaa			
i-OATP2-50	intron 5	1157	acagataatttttacttgtt	T/C	gtgcttttctgtatgatatg			
i-OATP2-51	intron 5	1226	ccttgattgtaataatctcc	A/C	cA/Ctgccaagagtggggccag		+	
i-OATP2-52	intron 5	1228	ttgattgtaataatctccA/Cc	A/C	tgccaagagtggggccaggt		+	
i-OATP2-53	intron 5	1304	actgttctcgtggtaatgaa	G/T	aagtctcacaagatctgatg		+	
i-OATP2-54	intron 5	1348	ttataaatgagagttcccct	G/A	caaaagctctcttgcctgcc		+	
i-OATP2-55	intron 5	1407	ttgctcttccttcatcttcc	G/A	ccatgattgtgaggcccccc		+	
i-OATP2-56	exon 6	521	gtcatacatgtggatatatg	T/C	gttcatgggtaatatgcttc	Val174Ala		

Table 1. Continued

ID	Region	Position[a]	Flanking sequence[b]	Variation (5' to 3')[c]	Flanking sequence[b]	Substitution	Repetitive sequence[d]	Identity to dbSNP
i-OATP2-57	exon 6	571	gggagactcccatagtacca	T/C	tggggctttcttacattgat	Leu191Leu		
i-OATP2-58	exon 6	597	ctttcttacattgatgattt	C/T	gctaaagaaggacattcttc	Phe199Phe		
i-OATP2-59	intron 7	33	agaacaaggtaccatgataa	C/T	gtctttctaagcacacatgc			
i-OATP2-60	intron 7	267	caaaataaccaaatgtaaaa	T/A	gtctccctcccaaactgact			
i-OATP2-61	intron 7	1260	gtaatctcacatttctctgc	A/G	tttacacttggtaaaacttt			
i-OATP2-62	intron 7	1386	agtctcaaattaatagccaa	G/A	agcatgcctttattgtaacc			dbSNP ID:rs2169970
i-OATP2-63	intron 7	1472	ctttaccacatgacagaatg	G/A	catgttcttagcaaataata			dbSNP ID:rs1000691
i-OATP2-64	intron 7	1697	tttacatgttcaattttaga	C/A	atatgccttagagtagctac			dbSNP ID:rs999278
i-OATP2-65	intron 7	2273	ttctcacgtcctatctagcg	C/T	gattatgacccttagttact			
i-OATP2-66	intron 8	207	gtggaagagaattaggtttg	T/C	actttttagcagggagaaac			
i-OATP2-67	intron 8	546	tcgggagaagtttctcccta	T/C	gtaattagagtaatatttA/Ct			
i-OATP2-68	intron 8	565	aT/Cgtaattagagtaatattt	A/C	ttttggtaattatctatcta			
i-OATP2-69	intron 8	668	taagtaatgtaaattaggat	G/T	catcagcatttgacagtgcc			
i-OATP2-70	intron 8	739	tggagaaccattgagagtca	A/G	taaacaaagagaatgacttg			
i-OATP2-71	intron 8	2193	tgatcacagatccaaatgac	A/G	taatttctaccatgaacaga			dbSNP ID:rs1871395
i-OATP2-72	intron 9	112	attttagtaatacaggataa	G/C	tataattttcttgtattctt			
i-OATP2-73	intron 9	266	ttagaggtagtatctgtata	A/G	ttggatcttataatttagtg			
i-OATP2-74	intron 9	305	tgctaagatctgagacaaac	C/G	cttttgtaattataatcatt			
i-OATP2-75	intron 9	888	aggttctgtatgtttttaa	T/C	aaatgacaaagatatattaa			dbSNP ID:rs1564364
i-OATP2-76	intron 11	10224	tacacttgttccataaaaaa	T/C	tcctctatattattcctagt			
i-OATP2-77	intron 11	10359	attaatagattcaacgtgag	G/C	ttcccttaaactttagccta			
i-OATP2-78	intron 11	10916	cttatatagaaagaaatcca	C/G	aaaactattttacctttat			
i-OATP2-79	intron 11	10997	aatatattagtttgaacaag	T/C	gagacttcactaaatataat			
i-OATP2-80	intron 11	11018	gagacttcactaaatataat	G/A	caatgtatttgcagcactgt			
i-OATP2-81	intron 12	442	aacattccaaaacttttaat	C/T	gaC/TtC/Aacagcatgactttta			
i-OATP2-82	intron 12	445	attccaaaacttttaatC/Tga	C/T	tC/Aacagcatgacttttataa			
i-OATP2-83	intron 12	447	tccaaaacttttaatC/TgaC/Tt	C/A	acagcatgacttttataata			
i-OATP2-84	intron 12	907	aatgaaaagaagctggcaga	T/C	tgaaacatactgaatgagag		+	
i-OATP2-85	intron 13	65	tatatatatatatatatata	C/T	acacacacatacatatatta		+	
i-OATP2-86	intron 13	870	aattctgagtatcctatttc	G/A	atgtatccaatctgtggcac			
i-OATP2-87	intron 13	1935	taaaaaaaaaaaaagtctgc	T/C	tttacagcaattgagccaag			
i-OATP2-88	intron 13	2261	aacgaatcctccaaattttt	G/C	aacttttatttaatcaaaat			
i-OATP2-89	intron 14	248	tcaaggataataaccaactt	G/A	tcaaaaatcagagataatag		+	
i-OATP2-90	intron 14	2463	atttgtttactaatatggaa	C/G	cttcttcaagacatattttt			
i-OATP2-91	intron 14	2857	tcatcatgtatttccaggac	A/T	cctggcaagatgctcctcag			
i-OATP2-92	intron 14	11458	atctccagaggtcctgctgt	C/T	tccccaaagtccactgaccc			
i-OATP2-93	3' untranslated region	2243	ataataaaacaaactgtagg	T/C	agaaaaaatgagagtactca			
i-OATP2-94	3' untranslated region	2404	tcttaataaaacaaatgagt	A/G	tcatacaggtagaggttaaa			
i-OATP2-95	3' untranslated region	2515	cagagtttgaactataatac	T/G	aaggcctgaagtctagcttg			
i-OATP2-96	3' untranslated region	2539	gcctgaagtctagcttggat	A/G	tatgctacaataatatctgt			
i-OATP2-97	intron 1	457-458	taattggcaaacataaaaaa	A/ins	caggtgtctcaaagtcacat			
i-OATP2-98	intron 1	7537-7538	gatcagcattacaaccaaga	G/ins	atggagaatgacattcagga			
i-OATP2-99	intron 1	10032-10035	tgtgtgattctatattactt	ACTT/del	gtttcaaatttctctccaca		+	
i-OATP2-100	intron 1	10058-10061	ttcaaatttctctccacaaa	TTTA/del	tttttctattaaattgtaat		+	
i-OATP2-101	intron 2	413-423	acttatttaaaaattctttt	$(A)_{11-13}$	caaaaaacaggatttaaaaa		+	
i-OATP2-102	intron 3	1595-1603	ttgccaagtaattcaagtgc	$(T)_{8-10}$	gtatttaaaacaacttttca			
i-OATP2-103	intron 4	10-23	ttcatgggatagtaagtgtt	$(A)_{12-14}$	cctctgtgccactatcagta			
i-OATP2-104	intron 5	1567-1572	gtgaatataaattacttgta	CTTGTA/del	aattaaaaaaaaataagtag			
i-OATP2-105	intron 5	1577-1585	attacttgtacttgtaaatt	$(A)_{9-10}$	taagtagaataattaagagt			

Table 1. Continued

ID	Region	Position[a]	Flanking sequence[b]	Variation (5' to 3')[c]	Flanking sequence[b]	Substitution	Repetitive sequence[d]	Identity to dbSNP
i-OATP2-106	intron 8	1939-1941	ttctctaactccttctactc	CTT/del	atttcaagcagatgcaactg			
i-OATP2-107	intron 10	3077-3078	aaattctttatctacttttt	CTT/ins	ttccctctttctctgctttc		+	
i-OATP2-108	intron 11	11011	aacaagT/Cgagacttcactaa	A/del	tataatG/Acaatgtatttgca			
i-OATP2-109	intron 12	1160-1169	agcatgacatggtagagatg	$(A)_{9-11}$	gcatttttaacatttgttaa			
i-OATP2-110	intron 12	1310-1312	tccatcttaatataaaatgt	TGT/del	ctactcaaaaggagaagtct			
i-OATP2-111	intron 13	9-34	tacgagcactaggtatgatg	$(A)_{24-27}$	tatatatatatatatatata		+	
i-OATP2-112	intron 13	35-64	aaaaaaaaaaaaaaaaaaaa	$(TA)_{10-21}$	C/Tacacacacatacatatatt		+	
i-OATP2-113	intron 13	1379-1387	aaaattattcaccacaatac	$(A)_{8-10}$	caaagtaaagttatgaacac			
i-OATP2-114	intron 13	1916-1928	aattctcttaaaataatgtt	$(A)_{11-13}$	gtctgcT/Ctttacagcaattg			
i-OATP2-115	intron 14	588-596	caattatactttacctcttt	$(A)_{8-10}$	ctaatttcaaattcatatat			
organic anion transporter peptide 8 (*OATP8*)								
i-OATP8-1	5' flanking region	-1413	aataggggcttaataactct	G/C	aaacttatgatttctcatat			
i-OATP8-2	5' flanking region	-1345	gaatttatcctacagatatg	A/G	ccacacagaaaatgacatat			dbSNP ID:rs2138334
i-OATP8-3	intron 1	38962	atgaaattagtttaaaaata	G/A	caaccttaactatactcctc			
i-OATP8-4	intron 2	253	acagacttaccaacaaagaa	T/G	tatccttcccaaaatgtcta		+	
i-OATP8-5	intron 2	329	actcatggtttgcaaattaa	C/G	tttttaggaaactttatctc			
i-OATP8-6	intron 2	2568	ccattctggtgctttctttc	G/A	tgaaactattttccatcagt			
i-OATP8-7	intron 2	2679	ctcttattgctcttcttcca	T/C	gttttaatctaaataattta			
i-OATP8-8	intron 2	2753	caggaaactttcacaaagcc	C/A	ctaattaatttaagctccct			
i-OATP8-9	intron 2	3132	tggtttaatgtaggagagtt	T/C	accttcacagttaaattaca			
i-OATP8-10	intron 2	3193	aatgtcttgggcatatttgc	A/G	ttcatttggggcaT/Ctcagtt			
i-OATP8-11	intron 2	3207	atttgcA/Gttcatttggggca	T/C	tcagttctactagatacaaa			
i-OATP8-12	exon 3	334	gaactggaagtattttgaca	T/G	ctttaccacatttcttcatg	Ser112Ala		
i-OATP8-13	intron 3	76	agaattttatttttatactt	G/A	taagtgggcagttacctttt			
i-OATP8-14	intron 3	2443	tcaatttcatgttgctctta	C/T	agttataggtattctaaaga			
i-OATP8-15	intron 4	67	taatcacgtctataaagttt	C/G	tgatattctttaacaaaatt			
i-OATP8-16	intron 4	91	tattctttaacaaaattgat	T/A	taagaacaaataggaagaac			
i-OATP8-17	intron 4	197	ggtttgaactgcacctgttc	G/A	cttatatgcagcttttgtcc		+	
i-OATP8-18	intron 4	813	tttaacagaataaaaaaaaa	T/A	attttgtaacgacaaaagaa			
i-OATP8-19	intron 4	974	atatgcaccttaaaaataac	C/G	tggatttttaaatatgtaat			
i-OATP8-20	intron 4	1003	taaatatgtaatgtacataa	G/T	gaatattatgcatattttgt			
i-OATP8-21	intron 6	155	cattaataatcagaataaaa	A/G	agaaatttagctcctattta			
i-OATP8-22	intron 6	750	atccaactggggtttagatt	T/G	cctctttctgcctctcctcc			
i-OATP8-23	intron 6	780	gcctctcctccatctgcacc	C/T	tctcttttcctcagcaaaca			
i-OATP8-24	intron 6	1248	ctatgccctgtaatctcaca	C/T	ttccctttatttaaaattgg			
i-OATP8-25	intron 6	1500	tcgtgtctgtgttagcatat	A/G	ataactcatcagggtttgtg			
i-OATP8-26	intron 6	2008	ataacataaatgagtaaaga	A/G	tatcaagggcaggaaattag			
i-OATP8-27	intron 6	2087	actactctccccatacacac	T/C	aaaactcatgtgctccccag			
i-OATP8-28	intron 6	12305	tcatctatggaggactgcaa	T/C	cattatcattatttcccaga			
i-OATP8-29	intron 7	363	taacaaatgataccagccat	C/G	atactattctctggtaatag			
i-OATP8-30	intron 7	411	cctttatttttgagaacct	G/A	gtggatgatattaagaC/Agta			
i-OATP8-31	intron 7	428	cctG/Agtggatgatattaaga	C/A	gtatatagatcactgtaata			
i-OATP8-32	intron 7	634	aaaattatatatatacatat	A/G	taatcttacctaagtattca		+	
i-OATP8-33	intron 7	1791	tgtttttttaagggtagtga	T/C	gtgaatagtaaagcgaattt			
i-OATP8-34	intron 7	2000	agttgagcaaattgctctca	G/A	gtagcataatgtcacttgaa			
i-OATP8-35	intron 7	2043	gtttattgatccatttttta	A/G	tggatcaacattgtagtgag			
i-OATP8-36	intron 7	2171	atttattttgagcaaaggtc	G/A	cG/AactctC/Tttagaaagcctc			
i-OATP8-37	intron 7	2173	ttattttgagcaaaggtcG/Ac	G/A	actctC/Tttagaaagcctcac			

Table 1. Continued

ID	Region	Position[a]	Flanking sequence[b]	Variation (5' to 3')[c]	Flanking sequence[b]	Substitution	Repetitive sequence[d]	Identity to dbSNP
i-OATP8-38	intron 7	2179	tgagcaaaggtcG/AcG/Aactct	C/T	ttagaaagcctcacaaatca			
i-OATP8-39	intron 7	2219	atttgtaactttaagtctta	T/G	ataacttatatttacaaaat		+	
i-OATP8-40	intron 7	2261	cagatattaatatatatttt	A/T	ttattgaaatatgttatttt		+	
i-OATP8-41	intron 8	150	acaaaatttctccatcttgt	T/C	ataT/Acatcgttgttctgcat			
i-OATP8-42	intron 8	154	aatttctccatcttgtA/Gata	A/T	catcgttgttctgcatttga			
i-OATP8-43	intron 8	1303	tttttttgagatggagtct	C/T	gctctgttgcccaggctggg		+	
i-OATP8-44	intron 8	1372	aagctccgcctcccaggttc	T/G	ccacccttctcttaaagaaa		+	
i-OATP8-45	exon 9	1272	tccttcttgtttcaacttct	A/G	tatttccctctaatctgcga	Leu424Leu		
i-OATP8-46	intron 10	63	tcacagatttgatttaataa	A/T	tacttatcaaatcttcctat			
i-OATP8-47	intron 10	911	cttgcccaatatcctaccaa	C/T	gtattattaaacggcatgga			
i-OATP8-48	intron 10	972	tcctagtttccttgaagata	G/A	gctacaactttagtaaactt			
i-OATP8-49	intron 10	1101	tccctggtcctgtgttgtcc	A/T	gT/Cagtgaagacctgaaagag			
i-OATP8-50	intron 10	1103	cctggtcctgtgttgtccA/Tg	T/C	agtgaagacctgaaagagag			
i-OATP8-51	intron 10	2027	cccattttcatgagtggcta	A/G	G/Attttgtcccgtttcaaact			
i-OATP8-52	intron 10	2028	ccattttcatgagtggctaA/G	G/A	ttttgtcccgtttcaaacta			
i-OATP8-53	intron 10	2148	gtattttggaaagaaaatgt	A/G	ggtggaagagaaatatttta		+	dbSNP ID:rs2053095
i-OATP8-54	intron 10	2214	atatacagaatttcatacac	T/C	aatttcttaaattcctaaat		+	dbSNP ID:rs2053096
i-OATP8-55	intron 10	2316	taaatattttagtttgagac	T/G	tctttaaatataatggaatg			dbSNP ID:rs2053097
i-OATP8-56	intron 10	2372	tgtatttggcaaatgtattt	G/T	ttaatatttcaaaaactatt			
i-OATP8-57	exon 11	1557	cagaacagaaattactcagc	A/G	cacttgggtgaatgcccaag	Ala519Ala		dbSNP ID:rs2053098
i-OATP8-58	intron 11	147	tttcttagaattattttgat	A/C	tttcaataacatcattaata			dbSNP ID:rs2053099
i-OATP8-59	intron 11	10339	aaaaaactgcattttagtgg	G/C	ttagctagaaaagatttgT/Gc			dbSNP ID:rs980084
i-OATP8-60	intron 11	10358	gG/Cttagctagaaaagatttg	T/G	ctcatatacacaataaatta			dbSNP ID:rs980085
i-OATP8-61	intron 11	10538	caacagaggatcaatgtaaa	T/G	gaaatctcttaaattaaaca			
i-OATP8-62	intron 12	55	ataaatattaatgttaaata	C/T	taaagactgaatgcaattaa		+	
i-OATP8-63	intron 12	1802	taaaatgaatcggtaaaaca	T/G	tcatgtataaatcactgtca			
i-OATP8-64	intron 12	2612	ataggcatataatactcttt	C/A	ttccctctgtatatagggag			
i-OATP8-65	exon 13	1833	aacagctgtggagcacaagg	G/A	gcttgtaggatatataattc	Gly611Gly		
i-OATP8-66	5' flanking region	-1590 to -1587	tacataacatatacctatat	CTAT/del	gttatgtgtctgcttatata			
i-OATP8-67	5' untranslated region	-28 to -11	agcatcagcaacaattaaaa	ATATTCACTTGGTATCTG/del	tagtttaataatggaccaac			
i-OATP8-68	5' untranslated region	-7 to -4	tattcacttggtatctgtag	TTTA/del	ataatggaccaacatcaaca			
i-OATP8-69	intron 4	213-214	ttcG/Acttatatgcagctttt	T/ins	gtccaaccaaacagaaggag		+	
i-OATP8-70	intron 4	505	tataactttctctttataaa	G/del	atgcaaaatgttatagcatt			
i-OATP8-71	intron 4	616	aatgaagtggaggaaaaaaa	A/del	tgatttcaagttttctgtct			
i-OATP8-72	intron 4	804-812	acatccatgtttaacagaat	$(A)_{9-11}$	T/Aattttgtaacgacaaaaga			
i-OATP8-73	intron 4	855	agattgtttaaccaaattag	G/del	aaactattattcaacacact			
i-OATP8-74	intron 7	619-628	ttttatatatgaattaaaat	$(AT)_{4-5}$	catatA/Gtaatcttacctaag		+	
i-OATP8-75	intron 7	1773-1779	attttctatattatgaactg	$(T)_{7-8}$	aagggtagtgaT/Cgtgaatag			
i-OATP8-76	intron 8	1270-1290	tagtgtgccacccttctctc	$(T)_{19-23}$	gagatggagtctC/Tgctctgt		+	
i-OATP8-77	intron 10	665	aactcaaaggctttttttt	T/del	ccatgtgacacatatcctgt			
i-OATP8-78	intron 11	247-250	aaaaatcttaaggcacacac	TGAT/del	tgacagttgccttgattgta			
i-OATP8-79	intron 12	1622-1630	aaataaattgttggcatcta	$(T)_{8-10}$	atttttctaagggtcgctgt			
i-OATP8-80	3' untranslated region	2464-2465	cctgatgcctttaaaaaaaa	A/del	tgaaacactttggatgtatt			
NADH:ubiquinone dehydrogenase flavoprotein 1 (*NDUFV1*)								
i-NDUFV1-1	intron 3	670	ctgggtggagtggggtggca	T/C	ggagttgaagacccagtcct			
i-NDUFV1-2	intron 6	160	tgtgccggccccagccctga	C/G	catgcatccctttggggacc			
i-NDUFV1-3	intron 9	27	accacccttctgcgtagcac	G/A	gagggtgggtggcatcaagg			
i-NDUFV1-4	3' flanking region	1111	tgtaggctgaggtcagcccc	A/C	atccagtccaaagcccaccc			

Table 1. Continued

ID	Region	Position[a]	Flanking sequence[b]	Variation (5' to 3')[c]	Flanking sequence[b]	Substitution	Repetitive sequence[d]	Identity to dbSNP
i-NDUFV1-5	3' flanking region	1658	gaatgcggaagtgctctgtg	G/A	gcacccaccatgctccgggc			
i-NDUFV1-6	3' flanking region	1713	gatctggggcggagggtaca	C/T	ggggctggcgctgggtgaag			
i-NDUFV1-7	intron 4	214	tggtgtaaattttttttttt	T/del	gcttcaaaaatatagtattt			
i-NDUFV1-8	3' flanking region	772-774	tgaactcggggttcagggtc	TTC/del	ctgtgaacactggttttgaa			
NADH:ubiquinone dehydrogenase flavoprotein 2 (*NDUFV2*)								
i-NDUFV2-1	intron 1	526	ggaaatgctggctaaataaa	C/T	ggtatcaaactaactctgaa			
i-NDUFV2-2	intron 1	6689	tcgttggatggtagtattgt	T/G	tgaacaacagaagaaattca			
i-NDUFV2-3	intron 1	14767	ccaaatgcatgccagcagag	C/T	gtggcaggaaggtacacaag			
i-NDUFV2-4	exon 2	86	aaggaatttgcataagacag	C/T	tatgcaaaatggagctggag	Ala29Val		
i-NDUFV2-5	intron 2	-29	cagaagatcttactctctaa	T/G	gaagctggataacacttttt			
i-NDUFV2-6	intron 2	-168	tttactttggtaatcatact	T/C	atcaaatgtgtgtttagaca			
i-NDUFV2-7	intron 4	677	aaaccacatactatttgatt	C/A	tgatgagaatcacataacca			
i-NDUFV2-8	intron 4	2295	tatgattcaactttcaaaag	A/T	gtattgtgatatgaaataga			
i-NDUFV2-9	intron 5	102	caacttctgccatcttattg	G/A	atctgtacttacctagtaat			
i-NDUFV2-10	intron 7	5466	tggtaagaggctttaagata	A/C	caaatgctcagctttcagga			
i-NDUFV2-11	intron 1	13562-13563	tactcttaaaattaatcctt	CTT/ins	ttattataagtatacagtct			
NADH:ubiquinone dehydrogenase flavoprotein 3 (*NDUFV3*)								
i-NDUFV3-1	5' flanking region	-606	aattacgactaacgttgggg	A/G	cgaactctttgctaaataaa			dbSNP ID:rs1573472
i-NDUFV3-2	5' flanking region	-222	cgccgcgcccccgccacagc	G/A	cccaggcgcccgcagggcac			
i-NDUFV3-3	5' flanking region	-111	tggccccaagggaggcactt	A/G	gccctactggggatgcgcgc			
i-NDUFV3-4	intron 1	137	ttgggccgctgaccccgctc	C/T	ctgggcccaggactgaccgc			
i-NDUFV3-5	intron 2	152	tatacaagacacaagatcta	T/C	aacagattttagaccaaaca			
i-NDUFV3-6	intron 2	6304	ttcacagatgaaggggttcc	G/A	aaatttttgtcaagaaagac			
i-NDUFV3-7	intron 2	6433	tcgccttcgtcttcatcctc	T/G	tccagctcctctgattctga			
i-NDUFV3-8	intron 2	6563	cctttgaaaacagagccccc	C/T	gagttacagtatcagcaaaa			
i-NDUFV3-9	intron 2	9619	actatcttctgtgcgcatgc	G/A	cagagcccaccttgcagagc			
i-NDUFV3-10	intron 2	9858	aggatgccagctctttaaat	G/A	agacatcgtttttgcttaac			
i-NDUFV3-11	intron 2	11673	cttggtaggtaagcgcctgt	A/G	tgtgagccaagtcattcata			

ins, Insertion polymorphism; del, deletion polymorphism; SNP, single-nucleotide polymorphism

[a] Nucleotide numbering is according to the mutation nomenclature (den Dunnen and Antonarakis 2000)

[b] 5′ and 3′ flanking sequences to each variation are denoted by small letters

[c] Variation is shown by capital letter

[d] + indicates the variation located with a repetitive sequence

drugs. The exon organization of each gene and locations of identified SNPs are illustrated schematically in Fig. 1 (see also Table 1). By comparing our data with SNPs deposited in the dbSNP database (National Center for Biotechnology Information [NCBI]), we determined that 236 (91.5%) were novel as of the middle of July 2001.

hOAT gene family

A total of 25 SNPs were identified from these three loci: 2 in 5′ flanking regions, 3 in 5′ untranslated regions, 3 in coding regions, 15 in introns, 1 in a 3′ untranslated region, and 1 in a 3′ flanking region. The genomic regions screened included 9.4 kb for *hOAT1*, 7.9 kb for *hOAT2*, and 13.5 kb for *hOAT3*; the distribution of SNPs in these three loci was one per 1232 bp on average. Frequencies of substitutions by type were 44% for A/G, 24% for C/T, 16% for A/C, 8% for C/G, 4% for G/T, and 4% for T/A. Regarding SNPs within coding elements (cSNP), all three such substitutions we detected among 96 Japanese chromosomes were synonymous: one was 1269C>T (Ser423Ser) in exon 7 of the *hOAT2* gene; the other two were in the *hOAT3* gene: 153G>A (Pro51Pro) in exon 2 and 723T>A (Thr241Thr) in exon 5. However, the two SNPs we found within the 5′ flanking region (putative promoter) of the *hOAT3* gene could affect the quantity of the gene product. We also found four insertion–deletion polymorphisms in the *hOAT1* and *hOAT3* loci.

hOATP gene family

A total of 206 SNPs were identified among the three *hOATP* loci: 12 in 5′ flanking regions, 9 in coding regions, 176 in introns, 5 in 3′ untranslated regions, and 4 in 3′ flanking regions. None were identified in 5′ untranslated regions. We screened 27 kb of genomic DNA for *hOATP1*, 36.5 kb for *hOATP2*, and 21.8 kb for *hOATP8*. The overall distribution of SNPs in this gene family was one per 414 bp, on average. The frequencies of different types of substitution were 36.9% for A/G, 27.2% for C/T, 7.8% for A/C, 9.2% for C/G, 11.2% for G/T, and 7.8% for T/A. Among the 9 SNPs located in coding regions, 4 would affect amino acid sequence: 388A>G (Asn130Asp) and 452A>G (Asn151Ser) in exon 5 and 521T>C (Val174Ala) in exon 6 of the *hOATP2* gene, and 334T>G (Ser112Ala) in exon 3 of the *hOATP8* gene. Tamai et al. (2000) had already reported two of these (Asn130Asp and Val174Ala in the *hOATP2* gene) in the process of cDNA cloning. It is not yet clear whether these SNPs affect transporter properties in hepatic excretion of drugs; a detailed genotyping study is required to clarify a relationship between these SNPs and functional properties of hOATP2 protein. According to an analysis of the promoter region of the *hOATP1* gene by Kullak-Ublick et al. (1997), *i-OATP1-1* is located within a putative HNF1-binding site, and *i-OATP1-3* is located in a region corresponding to a putative silencer element (-662/-440). In addition, *i-OATP1-46* (-188-189insA) is located in the minimal promoter region. These SNPs within 5′ flanking regions (putative promoters) could affect quantities of the gene products. We also found a total of 39 insertion–deletion polymorphsims among these three genes.

NDUFV gene family

Among the three *NDUFV* loci, we identified a total of 27 SNPs: 3 in 5′ flanking regions, 1 in a coding region, 20 in introns, and 3 in 3′ flanking regions. None were found in any 5′ or 3′ untranslated regions. We screened an 8.7-kb genomic region for *NDUFV1*, a 15.8-kb region for *NDUFV2*, and a 5.8-kb region for *NDUFV3*; distribution of SNPs was one in 1122 bp, on average. The substitutions in this gene family consisted of A/G (37%), C/T (33.3%), A/C (11.1%), C/G (3.7%), G/T (11.1%), and T/A (3.7%). The single SNP we found in a coding region changed alanine to valine at codon 29 in exon 2 of the *NDUFV2* gene. Hattori et al. (1998) reported that the frequency of homozygosity for valine at codon 29 was significantly higher in patients with Parkinson's disease than in control subjects (23.8% vs. 11.5%, Fisher's exact probability test, $p = 0.0099$). Computer analysis predicted that substitution at this residue is likely to alter the secondary structure of the gene product from an α-helix conformation in the C-terminal domain of the signal peptide to a β-sheet structure. Homozygosity for valine increases the risk of Parkinson's disease 2.4-fold. We identified three other types of variations in this gene family as well (Table 1).

The high-resolution map we are presenting here will serve as a useful resource for analyzing potential associations between variations at these nine loci and susceptibility to common diseases as well as efficacy and/or side effects of drugs. We believe that in the near future, using the SNP-based genotyping approach to predict individual differences in response to drugs on the basis of genetic factors will be a realistic approach to treatment of human diseases or toxic conditions. Finally, we hope that the virtual experiments made possible by our catalog will accelerate certain aspects of human genetic research.

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