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Identification of 779 genetic variations in eight genes encoding members of the ATP-binding cassette, subfamily C (*ABCC/MRP/CFTR*)

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Abstract We screened DNAs from 48 Japanese individuals for single-nucleotide polymorphisms (SNPs) in eight genes encoding the ATP-binding cassette, subfamily C (*ABCC/MRP/CFTR*), by direct sequencing of their entire genomic regions, except repetitive sequence elements. This approach identified 688 SNPs and 91 insertion/deletion polymorphisms among the eight genes. Of the 688 SNPs, 81 were identified in the *ABCC1* gene, 41 in *ABCC2*, 30 in *ABCC3*, 230 in *ABCC4*, 76 in *ABCC5*, 58 in *CFTR*, 102 in *ABCC8*, and 70 in *ABCC9*. Six SNPs were located in the 5′ flanking regions, 617 in introns, 46 in exons, and 19 in the 3′ flanking regions. These variants should contribute to studies that investigate possible correlations of genotypes with disease-susceptibility phenotypes and responsiveness or adverse effects to drugs.

Key words Single-nucleotide polymorphism (SNP) · ATP-binding cassette, subfamily C (ABCC) · Multidrug resistance protein (MRP) · Cystic fibrosis transmembrane conductance regulator (CFTR) · Sulfonylurea receptor (SUR)

Introduction

Multidrug resistance protein/cystic fibrosis transmembrane conductance regulator (MRP/CFTR) constitutes a subfamily of ATP-binding cassette (ABC) proteins (Human ABC Gene Nomenclature Committee [http://www.gene.ucl.ac.uk/nomenclature/genefamily/abc.html]). Members of the MRP/CFTR family have been recognized as export pumps for amphiphilic anions, particularly for conjugates of lipophilic compounds with glutathione or several other anionic residues (Keppler et al. 1998, 1999; König et al. 1999).

ABCC1 (MRP1) has been found to be overexpressed in many drug-resistant cell lines and tumor tissues (Cole et al. 1992; Loe et al. 1996). When being overexpressed in tumor cells, ABCC1 confers multidrug resistance by reducing intracellular drug concentrations in an ATP-dependent manner (Cole et al. 1994; Zaman et al. 1994). *ABCC1* is ubiquitously expressed, but at a very low expression level in the liver (Stride et al. 1996). This protein serves as an efflux pump for xenobiotics, drugs, and cellular metabolites (König et al. 1999). In the brain, ABCC1 together with ABCB1 (MDR1) forms part of the blood-brain barrier (Rao et al. 1999). Although various polymorphisms have been reported in the *ABCC1* gene, their phenotypic consequences have not been observed (Perdu and Germain 2000; Conrad et al. 2001; Ito et al. 2001).

ABCC2 (*MRP2*) is mainly expressed in the canalicular membrane of hepatocytes (Kool et al. 1997). Its major physiological function is the secretion of bilirubin glucuronides and organic anions into bile (Jedlitschky et al. 1997). ABCC2 also confers resistance to multiple anticancer chemotherapeutic agents when it is overexpressed in tumor cells (Cui et al. 1999). Mutations in the *ABCC2* gene were reported to cause Dubin-Johnson syndrome (Kartenbeck et al. 1996; Paulusma et al. 1997; Toh et al. 1999).

By screening an expressed sequence tag (EST) database, *ABCC3* (*MRP3*), *ABCC4* (*MRP4*), and *ABCC5* (*MRP5*) were identified (Kool et al. 1997). *ABCC3* is mainly expressed in liver, colon, intestine, and adrenal gland (Kool et al. 1997) and plays an important role in the removal of toxic organic anions from the liver under cholestatic conditions (Kool et al. 1999). *ABCC4* is widely expressed in human tissues and predominantly in the prostate (Lee et al. 1998), and its overexpression was shown to be correlated with ATP-dependent efflux of acyclic nucleoside monophosphates such as 9-(2-phosphonylmethoxyethyl) guanine

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and the anti-human immunodeficiency virus (HIV) drug 9-(2-phosphonylmethoxyethyl)adenine (PMEA) (Schuetz et al. 1999). Consequently, ABCC4 confers resistance to these drugs. *ABCC5* is mainly expressed at high transcript levels in skeletal muscle, brain, and heart, and at a very low level in liver (McAleer et al. 1999). This protein acts as the cellular export of cyclic nucleotides and introduces resistance to thiopurine anticancer drugs such as 6-mercaptopurine and thioguanine, and the anti-HIV drug PMEA (Wijnholds et al. 2000).

CFTR (cystic fibrosis transmembrane conductance regulator) acts as a chloride channel (Bear et al. 1992) and also regulates other ion transport pathways including the amiloride-sensitive epithelial sodium channel (Schreiber et al. 1999). Mutations in the *CFTR* gene were found in patients with cystic fibrosis (Cystic Fibrosis Mutation Data Base [http://www.genet.sickkids.on.ca/cftr/]) and congenital bilateral absence of the vas deferens (Costes et al. 1995; Zielenski et al. 1995). *CFTR* mutations were found at significantly higher frequencies in patients with disseminated bronchiectasis or allergic bronchopulmonary aspergillosis than expected (Miller et al. 1996; Pignatti et al. 1996).

The sulfonylurea receptor (SUR) contains ATP-sensitive potassium (K_{ATP}) channels (Aguilar-Bryan et al. 1995) that are involved in many diverse functions such as insulin secretion from pancreatic β cells, regulation of skeletal muscle excitability, neurotransmitter release, and smooth muscle relaxation (Quayle et al. 1997). The SUR subunit consists of two members, ABCC8 (SUR1) and ABCC9 (SUR2). Channels containing isoform ABCC8 (SUR1) found in neuronal cells and pancreatic β-cells are closed in response to the sulfonylurea hypoglycemic drugs (Gribble et al. 1998) and can be activated by diazoxide (D'hahan et al. 1999). Mutations and deficiencies in this protein were detected in patients with hyperinsulinemic hypoglycemia of infancy, an autosomal recessive disorder of unregulated and high insulin secretion (Thomas et al. 1995; Nestorowicz et al. 1996, 1998; Glaser et al. 1999; Verkarre et al. 1998). An arginine residue at codon 1273 was reported to be associated with hyperinsulinemia in Mexican American nondiabetic individuals (Goksel et al. 1998) and with type 2 diabetes mellitus in French Caucasians (Reis et al. 2000). ABCC9 (SUR2) is the primary regulatory subunit expressed in muscle cells and generates two splice variants, *SUR2A* (exon 38a) and *SUR2B* (exon 38b) (Isomoto et al. 1996). The *SUR2A* transcript was predominantly expressed in cardiac and skeletal muscle, whereas the *SUR2B* transcript was detected mainly in vascular smooth muscle (Isomoto et al. 1996; Davis-Taber et al. 2000).

To investigate the nature of apparent genotype/phenotype correlations for some ABC-transporters in more detail, we began by searching for additional single-nucleotide polymorphisms (SNPs) in the eight *ABCC* genes described earlier, including their promoter regions and introns, except repetitive elements. We report here a total of 779 genetic variations, of which 454 have not been reported before.

Subjects and methods

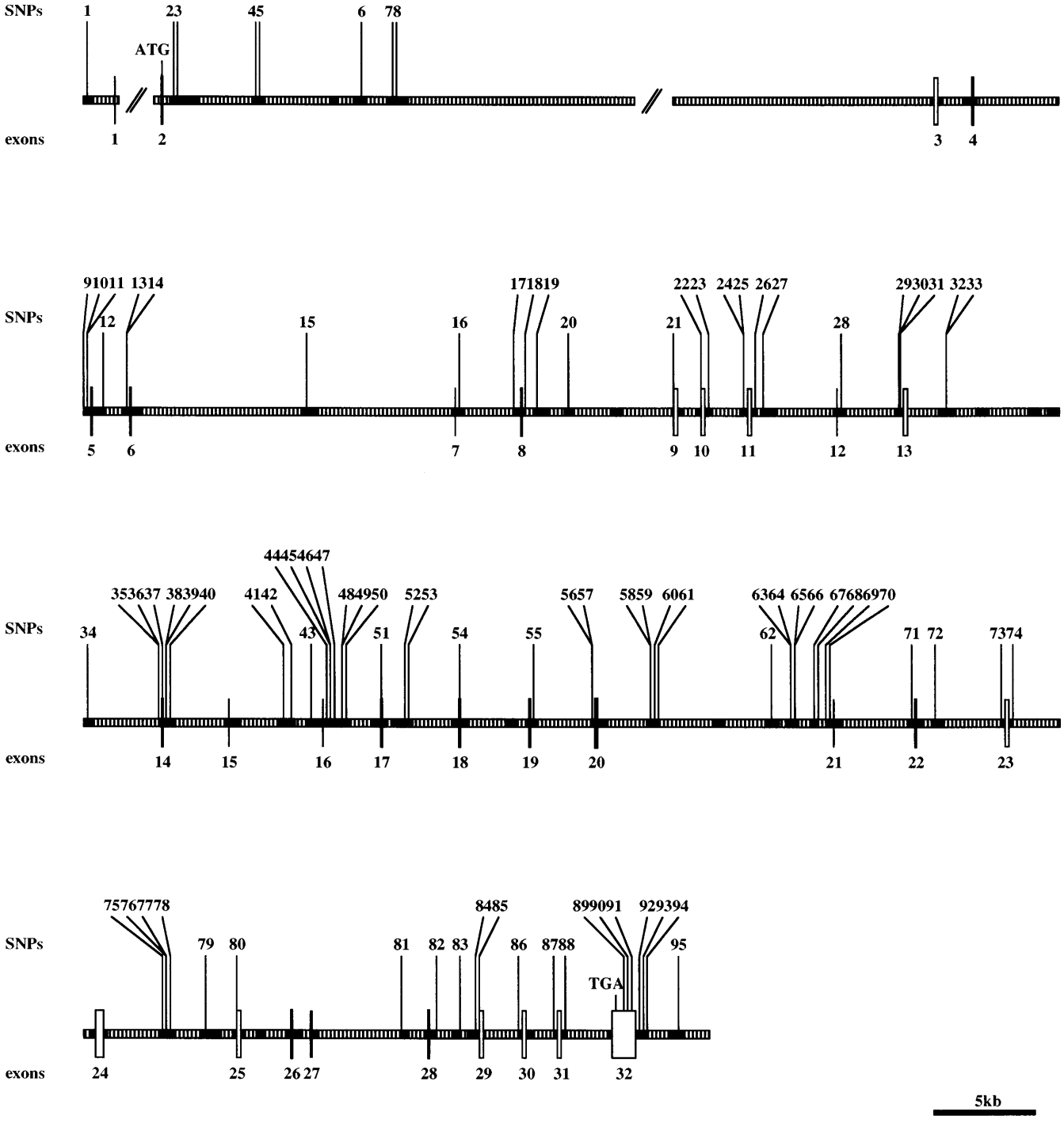
Total genomic DNAs were isolated from peripheral leukocytes by the standard phenol/chloroform extraction method in 48 unrelated Japanese individuals. Informed consent was obtained from each participant. On the basis of sequence information from GenBank, we designed polymerase chain reaction (PCR) primers to amplify DNA fragments from all eight genes, excluding repetitive elements, 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; Sekine et al. 2001; Saito 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 of the eight genes were defined by comparison of genomic sequences with cDNA sequences. Accession numbers of the genomic and cDNA sequences used for this study are listed in Table 1. We screened 96 Japanese chromosomes for SNPs in the eight *ABCC* genes by means of direct DNA sequencing. Figure 1 (a–h) illustrates the location of each variation in the respective genes; detailed information for nucleotide positions and substitutions is summarized in Table 2 (a–h).

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

Gene name	Chromosomal localization	Accession number			
		Genomic sequence			cDNA sequence
ABCC1	16p13.1	AC026452.5	AC025778.4		NM_004996.2
ABCC2	10q24	AL392107.4			U49248.1
ABCC3	17q22	AC004590.1	AC005921.3		NM_003786.2
ABCC4	13q32	AL356257.11	AL157818.12	AL139381.12	NM_005845.1
ABCC5	3q27	AC068644.5			NM_005688.1
CFTR	7q31.2	AC000111.1	AC000061.1		XM_004980.1
ABCC8	11p15.1	AC000406.1			NM000352.2
ABCC9	12p12.1	AC084806.9	AC008250.23		NM_005691.1



a

Fig. 1a–h. Locations of single-nucleotide polymorphisms (*SNPs*) in *ABCC1* (**a**), *ABCC2* (**b**), *ABCC3* (**c**), *ABCC4* (**d**), *ABCC5* (**e**), *CFTR* (**f**), *ABCC8* (**g**), and *ABCC9* (**h**) genes, indicated by *vertical lines*. *Open boxes* represent exons; *hatching* on the chromosomes indicates regions of repetitive elements. *ATG*, and *TGA* or *TAA*, initiation and stop codons, respectively; *ABCC*, ATP-binding cassette, subfamily C; *CFTR*, cystic fibrosis transmembrane conductance regulator

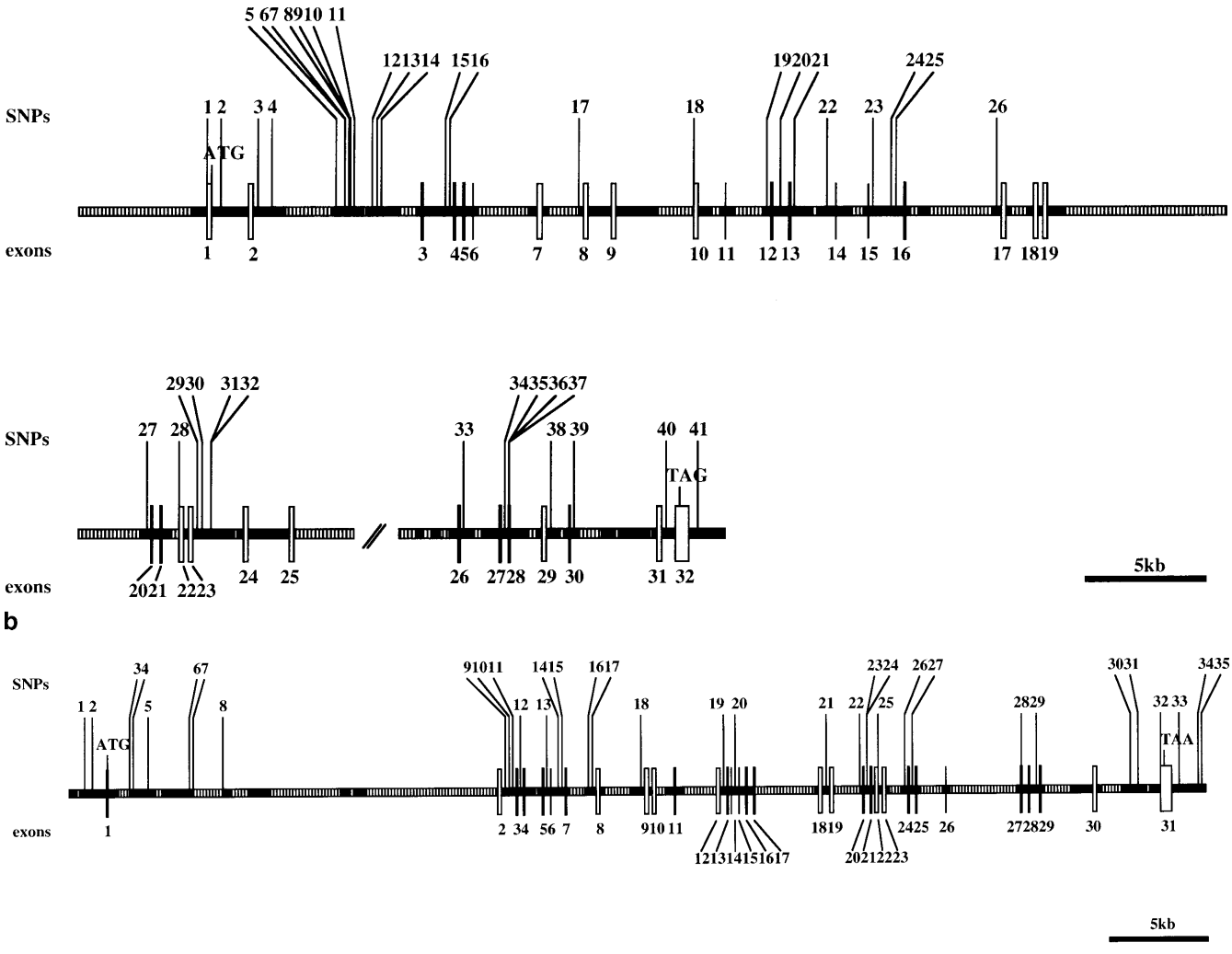


Fig. 1a–h. Continued

Resequencing of a total of about 423 kb of genomic DNA (37.7 kb for the *ABCC1* gene, 38.0 kb for *ABCC2*, 26.4 kb for *ABCC3*, 97.7 kb for *ABCC4*, 39.6 kb for *ABCC5*, 79.4 kb for *CFTR*, 50.0 kb for *ABCC8*, and 53.9 kb for *ABCC9*) identified a total of 688 SNPs and 91 insertion/deletion polymorphisms, as summarized in Table 3. On average, we identified 1 SNP in every 614 nucleotides. Four hundred fifty-four (58%) of the 779 genetic variations identified in our screening (including insertion/deletion polymorphisms) were not reported previously.

Among the 688 SNPs, 6 were located in the 5′ flanking regions, 617 in introns, 46 in exons, and 19 in 3′ flanking regions (Table 4). Among the 46 SNPs detected in exons, 3 were located in the 5′ untranslated region (UTR), 36 in coding regions, and 7 in 3′UTR. Of the 36 SNPs detected in the coding regions, 10 SNPs would cause substitution of an amino acid and 6 of them are novel. Among the 26 synonymous SNPs, 7 are novel (Table 5).

Tables 6 and 7 summarize the 39 genetic variations that are present in the regions surrounding the exon–intron junctions and that might introduce alternative splicing or influence the splicing machinery. Two polymorphisms (intron 19 + 3383 in the *ABCC1* gene, and intron 12 + 85 in *ABCC3*) were located within the putative branch point consensus sequence.

Discussion

We identified 779 genetic variations (688 SNPs and 91 insertion/deletion polymorphisms) by screening the entire genomic regions, except for repetitive sequences, encoding eight *ABCC* genes (*ABCC1, ABCC2, ABCC3, ABCC4, ABCC5, CFTR, ABCC8, and ABCC9*) in 48 unrelated Japanese individuals. Polymorphisms published here should be useful for examining the relationships between genotypes and susceptibility to certain diseases as well as for examining the efficacy or adverse effects of certain drugs. Among the six novel nonsynonymous polymor-

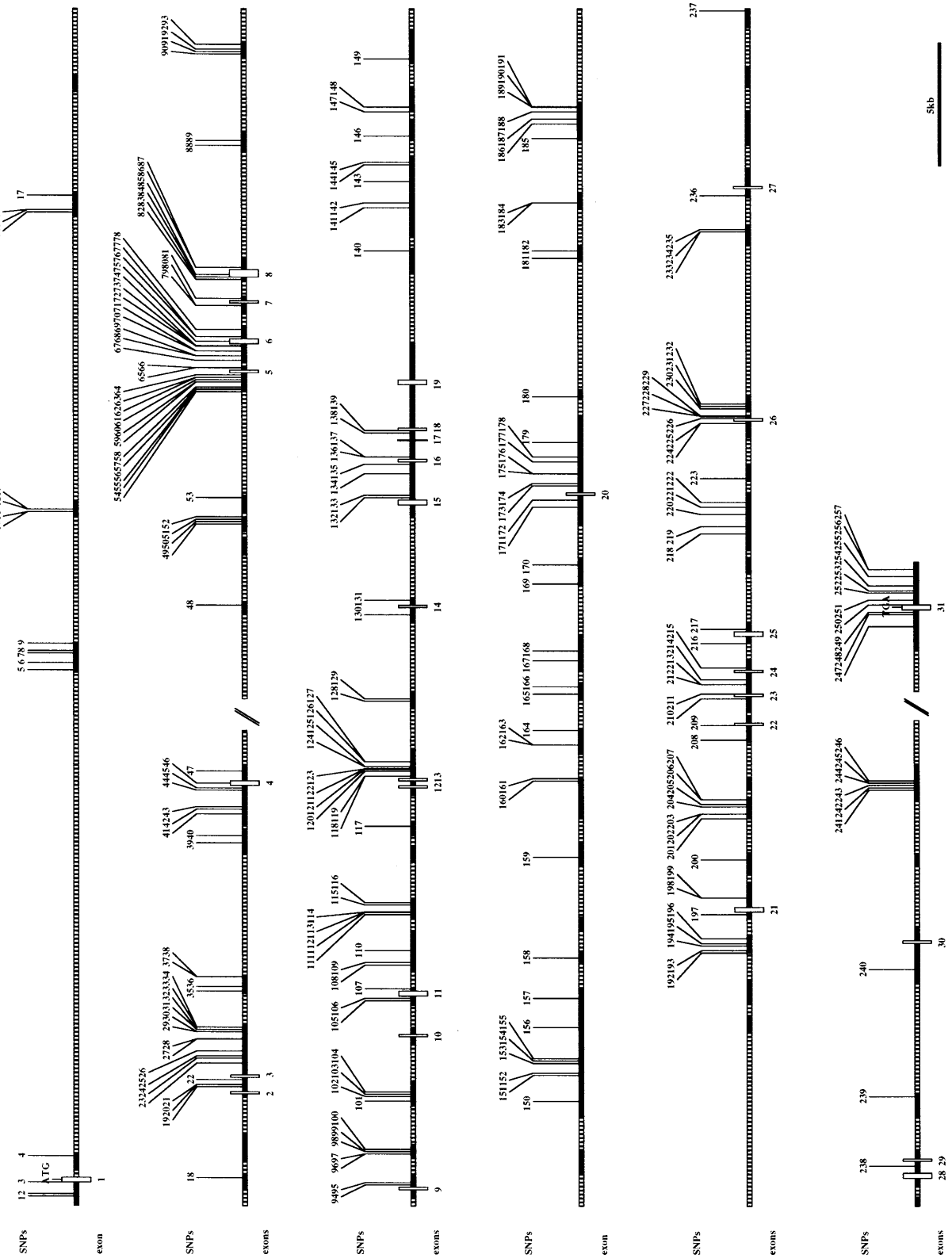


Fig. 1a–h. Continued

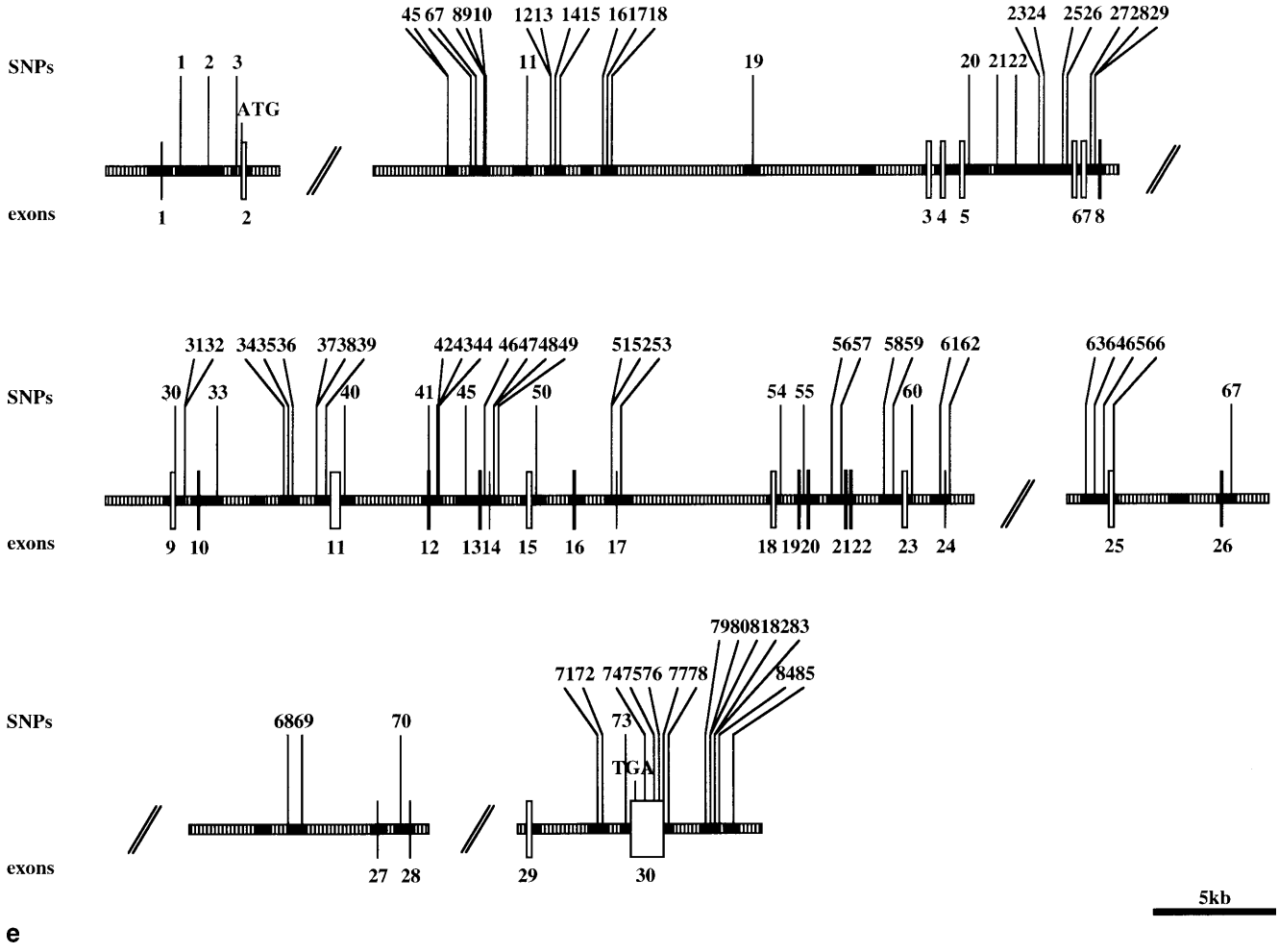
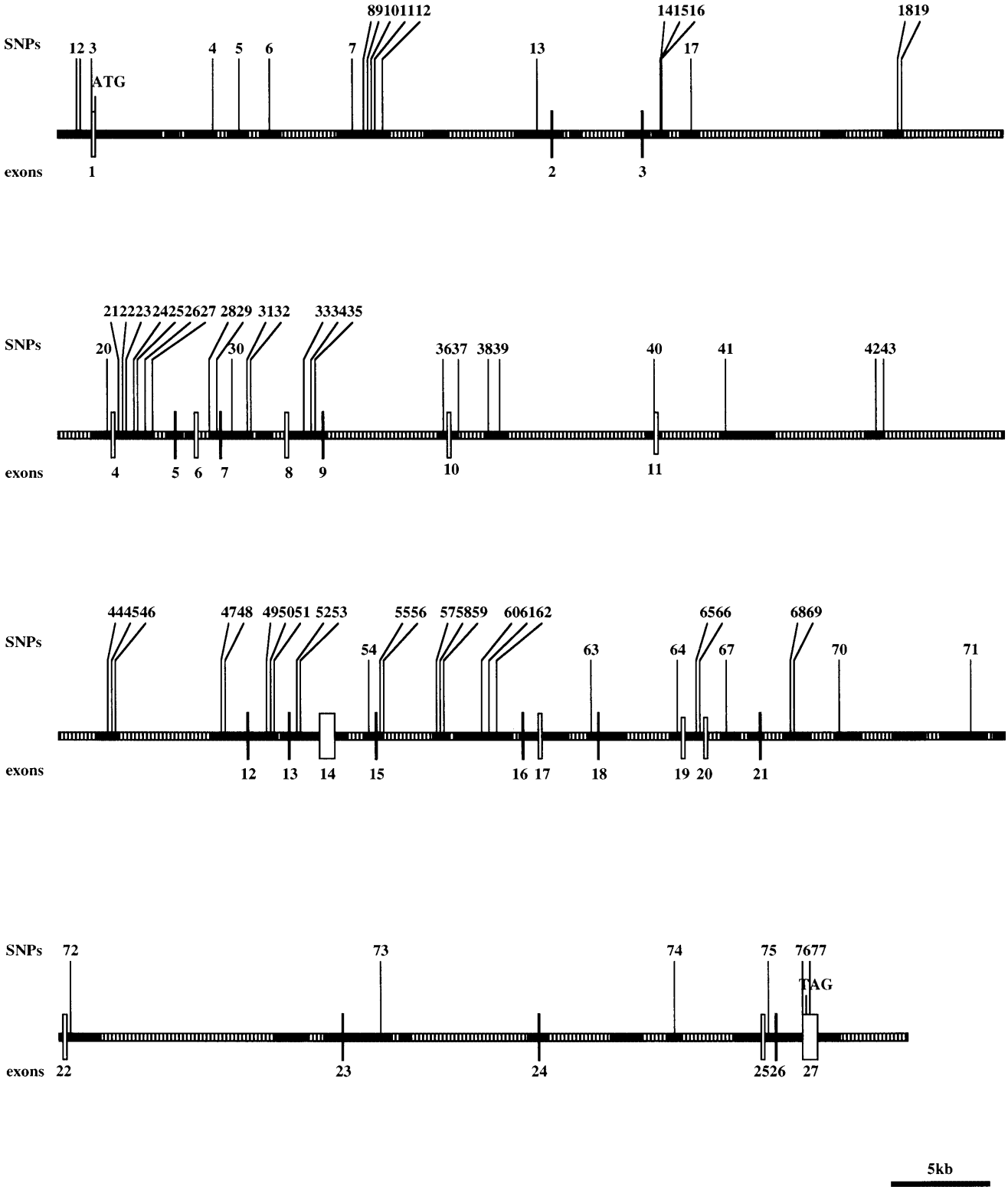


Fig. 1a–h. Continued

phisms, three SNPs (Cys171Gly and Glu757Lys in *ABCC4*, and Val560Met in *ABCC8*) present in the transmembrane domain and one SNP (Arg723Gln in *ABCC1*) in the nucleotide-binding domain may influence the function of the gene products and could have phenotypic consequences.

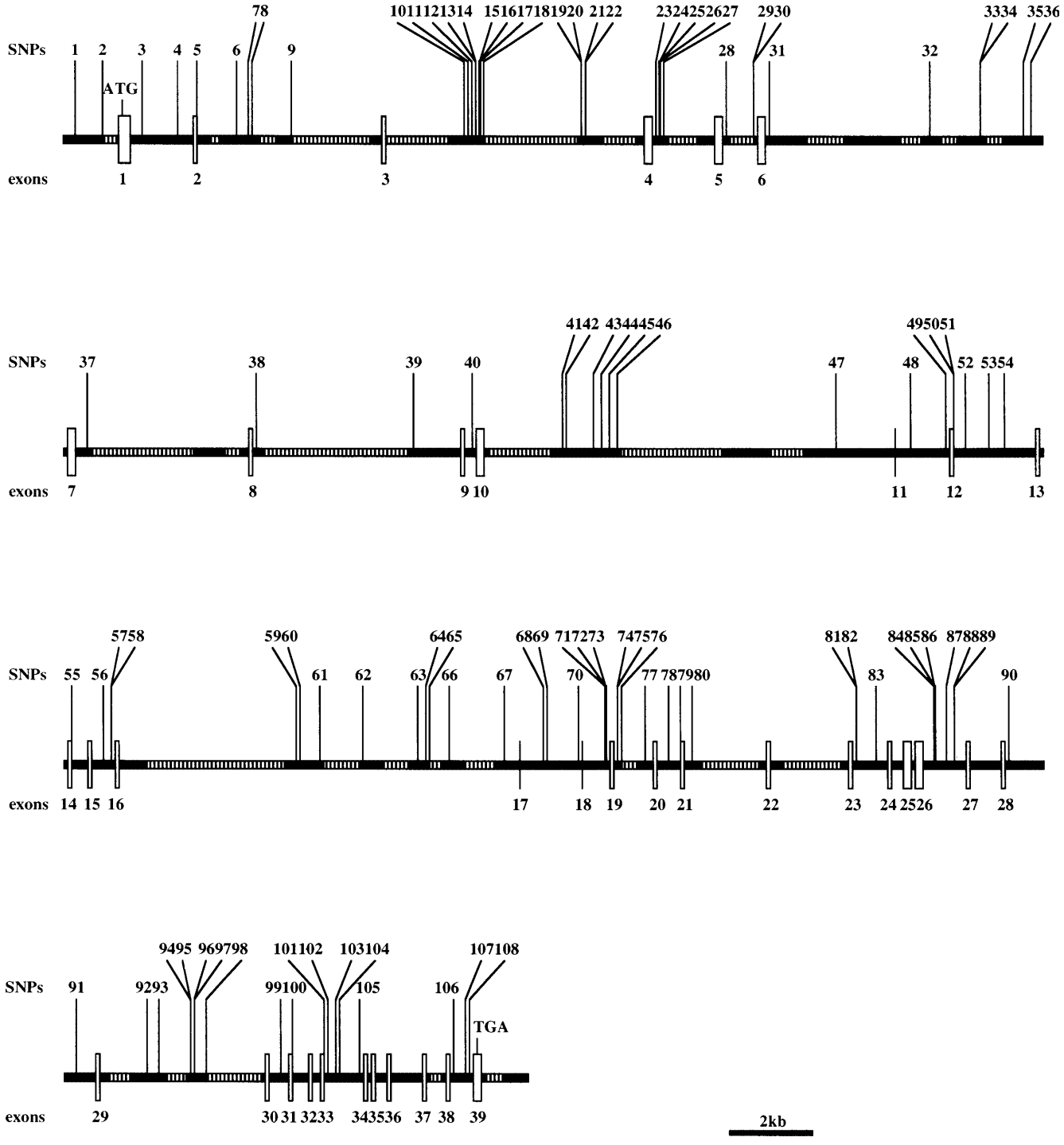
We identified many genetic variations within the intronic regions flanking the exon–intron junctions. These regions contained unique branch point sequences that are located 6–59 nucleotides upstream of the splice acceptor site and have the RNA consensus sequence YNYURAC (Y = C or T; R = G or A; N = any base) (Maquat 1996). A at position 6 in this consensus is critical for formation of a mammalian splice intermediate, the lariat structure. In addition, it has been shown that mutation of this A residue strongly reduces splicing efficiency of the downstream exon (Reed and Maniatis 1988). Two polymorphisms (Intron 19 + 3383 in the *ABCC1* gene, and Intron 12 + 85 in *ABCC3*) that we found are located within the putative branch point consensus sequence. Because these polymorphisms are located next to the A residue, these variants might influence mRNA processing.

In introns of most mammalian genes, the polypyrimidine tract near the splice acceptor site is highly conserved and plays a central role in aiding the splice branch site recognition, and in identifying and using the splice acceptor site (Smith et al. 1989; Reed 1989). For example, the deletion of the polypyrimidine tract inhibits spliceosome assembly and lariat formation (Reed and Maniatis 1985; Ruskin and Green 1985). In the *CFTR* gene, there were sequence variations of the TG dinucleotide repeats immediately followed by the polythymidine (poly-T) tract at the splice branch/acceptor site of exon 9 (although this exon was reported to be exon 9, it is in fact exon 10) (Chu et al. 1991). Although polymorphisms were reported in both the TG dinucleotide repeat and the poly-T tract in the Caucasian population, we found no polymorphism within the poly-T tract in the Japanese population. Chu et al. (1993) demonstrated that the shorter the poly-T tract at exon 9 splice/branch acceptor site of the *CFTR* gene, the higher the proportion of in-frame skipping of exon 9 in the transcript of the respiratory epithelium. Moreover, Cuppens et al. (1998) found that TG dinucleotide-repeat polymorphism independently affected the amount of the *CFTR* transcript lacking exon 9. A longer



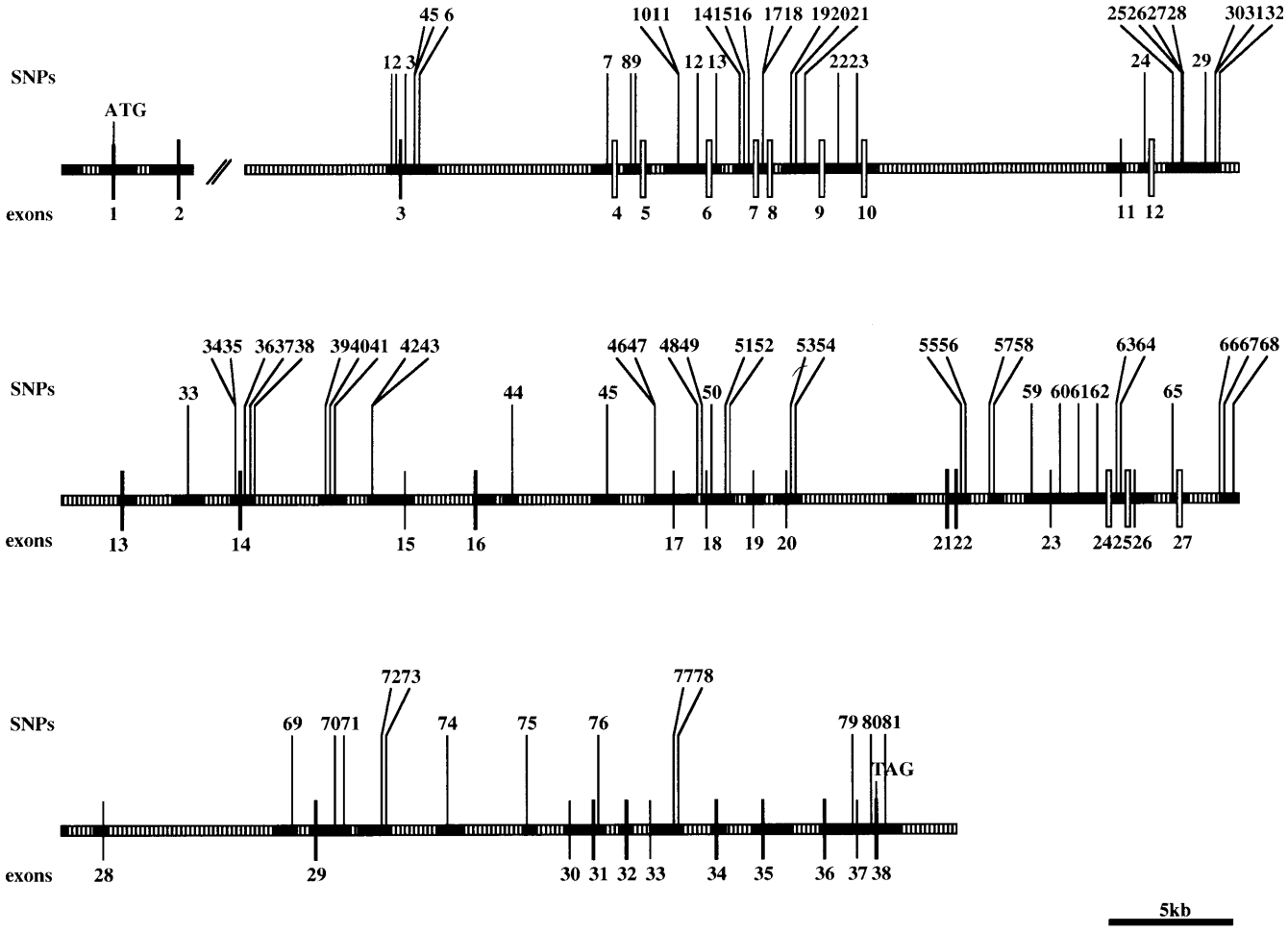
f

Fig. 1a–h. Continued



g

Fig. 1a–h. Continued



h

Fig. 1a–h. Continued

Table 2a. Summary of genetic variations detected in the *ABCC1* gene

No.	Location	Position[a]	Genetic variation	NCBI SNP ID
1	5′Flanking	−1661	A/G	
2	Intron 2	601	G/A	rs215109
3	Intron 2	635	T/C	
4	Intron 2	4769	G/del	
5	Intron 2	4834	G/A	rs1472532
6	Intron 2	10069	T/C	
7	Intron 2	11782	A/G	rs215096
8	Intron 2	(11965–11984)	$(T)_{18–20}$	
9	Intron 4	4302	T/G	
10	Intron 4	4394	A/C	
11	Intron 4	4524	T/C	
12	Intron 5	409	G/A	rs1967120
13	Intron 5	1759	C/G	rs185005
14	Intron 5	1768	T/C	rs246215
15	Intron 6	9045	G/A	
16	Intron 7	208	G/A	rs2062541
17	Intron 7	(3059–3071)	$(A)_{11–13}$	
18	Intron 8	54	C/A[b]	rs903880
19	Intron 8	(886–889)	GAAA/del	
20	Intron 8	2420	C/T	rs246230
21	Exon 9	16	T/C(Val275Val)[c]	rs246221
22	Exon 10	22	T/C(Asn354Asn)	rs35587
23	Intron 10	8	A/G	rs35588

Table 2a. Continued

No.	Location	Position[a]	Genetic variation	NCBI SNP ID
24	Intron 10	1940	C/G	rs35591
25	Intron 10	1953	T/C	rs35592
26	Intron 11	198	C/A	
27	Intron 11	784	C/G	
28	Intron 12	122	C/G	
29	Intron 12	(3138–3148)	$(A)_{10–12}$	
30	Intron 12	3197	G/A	rs35595
31	Intron 12	3227	C/T[c]	
32	Intron 13	2060	T/C	
33	Intron 13	(2061–2062)	C/ins	
34	Intron 13	7882	G/A	rs35597
35	Intron 13	11776	G/A	
36	Intron 13	11824	A/G	rs35604
37	Exon 14	7	T/C(Leu562Leu)[c]	rs35605
38	Intron 14	105	C/T	rs35606
39	Intron 14	179	A/T	
40	Intron 14	321	T/C	rs35607
41	Intron 15	2754	G/C	rs35620
42	Intron 15	3022	C/T	rs35621
43	Intron 15	3980	C/T	rs35625
44	Intron 16	219	G/T	
45	Intron 16	310	C/T	
46	Intron 16	357	G/T	rs35626
47	Intron 16	513	G/A	rs35627
48	Intron 16	848	A/G	rs35628
49	Intron 16	890	G/T	
50	Intron 16	1184	C/T	rs35629
51	Exon 17	19	C/T(Pro669Pro)	rs2301666
52	Intron 17	1171	G/A	
53	Intron 17	1332	A/G	
54	Exon 18	53	G/A(Arg723Gln)	
55	Intron 19	293	T/C	rs2074086
56	Intron 19	(3369–3374)	$(CA)_{2–3}$	
57	Intron 19	3383	G/C	rs207487
58	Intron 20	2730	C/T	
59	Intron 20	2789	G/C	
60	Intron 20	2919	C/T	
61	Intron 20	3024	C/T	
62	Intron 20	8716	G/A	rs2239996
63	Intron 20	9718	A/C	
64	Intron 20	9733	G/C	
65	Intron 20	(9895–9896)	AT/del	
66	Intron 20	9952	G/A	
67	Intron 20	11120	A/G	
68	Intron 20	11147	G/A	
69	Intron 20	(11629–11631)	CTT/del	
70	Intron 20	11864	C/T	
71	Intron 21	3860	G/del	
72	Intron 22	878	G/A	
73	Intron 22	(4428–4445)	$(GGGGCT)_{3–4}$	
74	Intron 23	62	T/C	
75	Intron 24	3171	C/T	
76	Intron 24	(3349–3368)	$(T)_{19–22}$	
77	Intron 24	3369	T/C	
78	Intron 24	3584	A/G	
79	Intron 24	5322	T/G	rs2238475
80	Exon 25	60	G/A(Pro1150Pro)	
81	Intron 27	4539	G/A	
82	Intron 28	179	G/A	rs212011
83	Intron 28	1354	G/A	rs212082
84	Intron 28	2150	G/A	rs212083
85	Exon 29	36	G/A(Ser1334Ser)[c]	rs2239330
86	Intron 29	1920	G/A	rs212087
87	Intron 30	(1708–1714)	$(T)_{6–7}$	
88	Intron 31	18	G/A[b]	rs212088
89	Exon 32	652	C/T(3′UTR)	
90	Exon 32	910	C/G(3′UTR)	rs129081

Table 2a. Continued

No.	Location	Position[a]	Genetic variation	NCBI SNP ID
91	Exon 32	975	T/A(3′UTR)	rs212090
92	3′Flanking	158	G/A	
93	3′Flanking	(187–199)	$(T)_{11–13}$	
94	3′Flanking	378	T/C	rs212091
95	3′Flanking	2227	G/A	

ABCC1, ATP-binding cassette, subfamily C, member1; NCBI, National Center for Biotechnology Information; SNP, single-nucleotide polymorphism; UTR, untranslated region; del, deletion; ins, insertion
[a]For SNPs in the 5′ flanking region, intron region, or 3′ flanking region, nucleotide positions are counted from the first intronic nucleotide at the exon/intron junction (for SNPs in the exon region, nucleotide positions are counted from the first exonic nucleotide at the exon/intron junction)
[b]SNPs previously reported by Conrad et al. (2001)
[c]SNPs previously reported by Ito et al. (2001)

Table 2b. Summary of genetic variations detected in the *ABCC2* gene

No.	Location	Position[a]	Genetic variation	NCBI SNP ID
1	Exon 1	77	C/T(5′UTR)	rs717620
2	Intron 1	413	A/C	rs2756103
3	Intron 2	192	T/G	
4	Intron 2	1020	G/C	
5	Intron 2	3639	C/A	
6	Intron 2	3930	A/G	
7	Intron 2	3989	C/T	
8	Intron 2	4078	T/C	rs2145852
9	Intron 2	4171	C/T	rs2756107
10	Intron 2	4257	G/A	rs2145853
11	Intron 2	4436	C/G	rs2180990
12	Intron 2	5227	A/G	
13	Intron 2	5373	A/G	
14	Intron 2	5538	G/T	
15	Intron 3	772	A/T	rs2073336
16	Intron 3	1145	C/T	rs2804400
17	Intron 7	1658	G/T	rs2756109
18	Exon 10	40	G/A(Val417Ile)	rs2273697
19	Intron 11	1672	T/A	
20	Intron 12	148	A/G	rs2073337
21	Intron 13	180	G/C	
22	Intron 13	1497	T/C	rs2756114
23	Intron 15	169	T/C	
24	Intron 15	949	A/G	
25	Intron 15	984	A/C	
26	Intron 16	4059	C/G	
27	Intron 19	10899	G/A	
28	Exon 22	51	G/A(Ser978Ser)	
29	Intron 23	56	C/T	
30	Intron 23	432	G/A	
31	Intron 23	734	G/A	
32	Intron 23	801	T/G	
33	Intron 26	154	T/C	
34	Intron 27	124	C/G	
35	Exon 28	52	A/C(Lys1299Gln)	
36	Exon 28	84	C/T(Tyr1309Tyr)	
37	Exon 28	129	C/T(Ile1324Ile)	
38	Intron 29	154	A/G	
39	Intron 30	91	T/C	
40	Intron 31	170	A/G	
41	3′Flanking	371	C/T	rs12826

ABCC2, ATP-binding cassette, subfamily C, member2

Table 2c. Summary of genetic variations detected in the *ABCC3* gene

No.	Location	Position[a]	Genetic variation	NCBI SNP ID
1	5′Flanking	−1064	C/T	
2	5′Flanking	−(827–820)	$(C)_{7–8}$	
3	Intron 1	1226	T/G	
4	Intron 1	(1389–1399)	$(A)_{10–12}$	
5	Intron 1	2070	C/T	
6	Intron 1	4378	A/G	rs1548529
7	Intron 1	4477	G/A	
8	Intron 1	6189	T/C	
9	Intron 2	268	G/A	
10	Intron 2	376	G/C	
11	Intron 2	446	C/T	
12	Intron 3	166	G/A	rs2301836
13	Intron 5	206	G/A	rs739923
14	Intron 6	432	G/C	rs733393
15	Intron 6	546	G/A	rs733392
16	Intron 7	1132	C/G	rs1978153
17	Intron 7	1537	C/T	rs2301837
18	Intron 8	2323	C/G	
19	Intron 12	85	C/del	
20	Intron 14	257	T/C	rs879459
21	Intron 18	303	G/A	rs2240801
22	Intron 19	1581	C/T	
23	Intron 20	29	C/T	rs2072365
24	Intron 20	53	G/A	rs2072366
25	Exon 22	180	C/T(Gly1013Gly)	
26	Intron 23	1053	G/A	rs2240802
27	Intron 24	84	C/T	rs967935
28	Exon 27	135	C/T(His1314His)	rs2277624
29	Intron 28	412	T/C	rs872793
30	Intron 30	1979	C/G	
31	Intron 30	2340	A/G	
32	Exon 31	34	A/G(Glu1503Glu)	rs1051640
33	3′Flanking	(555–558)	AAGA/del	
34	3′Flanking	1455	G/A	
35	3′Flanking	(1650–1659)	$(A)_{9–11}$	

ABCC3, ATP-binding cassette, subfamily C, member3

Table 2d. Summary of genetic variations detected in the *ABCC4* gene

No.	Location	Position[a]	Genetic variation	NCBI SNP ID
1	5′Flanking	−644	C/T	
2	5′Flanking	−527	C/G	rs869951
3	Exon 1	67	C/T(5′UTR)	
4	Intron 1	(864–865)	CT/del	
5	Intron 1	21255	A/G	
6	Intron 1	21503	T/C	
7	Intron 1	21900	C/G	
8	Intron 1	22005	C/T	
9	Intron 1	(22256–22264)	$(T)_{8–9}$	
10	Intron 1	27784	C/G	
11	Intron 1	27821	A/T	
12	Intron 1	27837	A/G	
13	Intron 1	27880	C/T	
14	Intron 1	40310	A/T	
15	Intron 1	40372	G/A	
16	Intron 1	40413	G/A	
17	Intron 1	40958	A/G	
18	Intron 1	50060	G/A	
19	Intron 2	181	G/T	
20	Intron 2	254	G/A	
21	Intron 2	290	T/C	
22	Intron 2	543	T/C	
23	Intron 3	557	G/A	
24	Intron 3	718	G/A	
25	Intron 3	801	G/A	
26	Intron 3	1022	T/C	

Table 2d. Continued

No.	Location	Position[a]	Genetic variation	NCBI SNP ID
27	Intron 3	1471	A/G	
28	Intron 3	1490	G/A	
29	Intron 3	(1833–1834)	G/ins	
30	Intron 3	1870	G/A	
31	Intron 3	1927	G/A	
32	Intron 3	1970	A/T	
33	Intron 3	2039	T/C	
34	Intron 3	(2067–2068)	CTTT/ins	
35	Intron 3	3563	G/A	
36	Intron 3	3696	C/G	
37	Intron 3	4093	T/C	
38	Intron 3	4097	T/del	
39	Intron 3	9724	A/G	
40	Intron 3	9988	G/A	
41	Intron 3	10952	A/G	
42	Intron 3	11125	A/G	
43	Intron 3	11244	C/del	
44	Intron 3	11916	A/del	
45	Intron 3	12047	A/G	
46	Exon 4	205	T/G(Cys171Gly)	
47	Intron 4	(412–414)	GTT/del	
48	Intron 4	−(9757–9756)	T/ins	
49	Intron 4	−6373	C/G	
50	Intron 4	−6267	T/C	
51	Intron 4	−6097	T/C	
52	Intron 4	−6057	C/T	
53	Intron 4	−5295	A/G	
54	Intron 4	−803	C/T	
55	Intron 4	−745	C/T	rs1678400
56	Intron 4	−736	C/T	
57	Intron 4	−728	C/T	
58	Intron 4	−624	A/C	
59	Intron 4	−470	C/T	
60	Intron 4	−411	G/A	
61	Intron 4	−323	C/T	
62	Intron 4	−246	A/G	
63	Intron 4	−199	C/T	
64	Intron 4	−108	C/T	rs899497
65	Intron 5	50	C/T	rs899496
66	Intron 5	73	C/T	
67	Intron 5	403	G/A	
68	Intron 5	537	T/A	rs943288
69	Intron 5	559	G/A	rs873706
70	Intron 5	749	G/A	rs873705
71	Intron 5	750	C/T	rs899495
72	Intron 5	937	G/C	
73	Intron 5	949	A/C	rs2389203
74	Intron 5	965	G/C	rs1678403
75	Exon 6	48	C/T(Ile223Ile)	rs899494
76	Intron 6	150	C/T	
77	Intron 6	158	C/T	rs2389204
78	Intron 6	(380–381)	AT/ins	
79	Intron 6	1400	T/G	rs2274410
80	Intron 6	1474	G/A	rs2274409
81	Intron 7	80	G/A	rs2274408
82	Intron 7	894	A/T	
83	Exon 8	1	G/T(Lys302Asn)	rs2274407
84	Exon 8	40	G/A(Arg317Arg)	rs2274406
85	Exon 8	58	G/A(Ser323Ser)	rs2274405
86	Intron 8	82	C/G	
87	Intron 8	100	C/T	
88	Intron 8	5212	A/T	
89	Intron 8	5444	T/G	
90	Intron 8	8969	A/G	
91	Intron 8	9106	T/C	
92	Intron 8	9189	G/A	rs1751021
93	Intron 8	9412	G/A	
94	Intron 9	70	T/C	rs2274403
95	Intron 9	116	A/G	
96	Intron 9	1384	T/C	

Table 2d. Continued

No.	Location	Position[a]	Genetic variation	NCBI SNP ID
97	Intron 9	1428	A/G	rs1751015
98	Intron 9	1459	A/G	
99	Intron 9	1485	C/A	rs1751014
100	Intron 9	1632	C/A	
101	Intron 9	3630	G/del	
102	Intron 9	3830	C/T	
103	Intron 9	3940	C/T	
104	Intron 9	4023	G/A	rs1678374
105	Intron 10	1411	A/G	rs1557069
106	Intron 10	1504	G/A	
107	Intron 11	171	C/A	rs2148529
108	Intron 11	1233	T/C	rs1564351
109	Intron 11	1293	G/A	rs1751008
110	Intron 11	1817	G/C	
111	Intron 11	3261	C/T	rs1887163
112	Intron 11	3322	C/A	rs1887162
113	Intron 11	3342	T/C	
114	Intron 11	3377	T/C	
115	Intron 11	(3610–3625)	$(A)_{15–17}$	
116	Intron 11	3737	A/G	
117	Intron 11	6953	C/A	
118	Intron 13	91	G/A	rs1751005
119	Intron 13	118	C/T	rs2296653
120	Intron 13	280	G/A	rs1678405
121	Intron 13	349	T/G	rs1073500
122	Intron 13	373	A/G	rs2009772
123	Intron 13	386	G/A	rs2478461
124	Intron 13	442	G/C	
125	Intron 13	459	T/C	
126	Intron 13	633	G/A	
127	Intron 13	645	G/T	
128	Intron 13	3092	C/T	rs1751003
129	Intron 13	3306	A/C	
130	Intron 13	6722	G/A	rs1729786
131	Intron 14	252	A/G	
132	Intron 15	124	C/T	
133	Intron 15	219	G/A	rs1729770
134	Intron 15	1016	A/G	rs1038138
135	Intron 15	1552	C/T	
136	Intron 16	107	T/C	rs1729764
137	Intron 16	157	G/A	
138	Intron 17	329	T/C	
139	Exon 18	56	G/A(Glu757Lys)	
140	Intron 19	5440	T/C	rs1729788
141	Intron 19	7202	T/del	
142	Intron 19	7445	T/C	
143	Intron 19	8337	T/C	rs1471481
144	Intron 19	9018	A/G	
145	Intron 19	9127	G/T	rs899498
146	Intron 19	10304	C/A	rs1479390
147	Intron 19	11388	A/G	
148	Intron 19	11646	T/del	
149	Intron 19	13517	A/T	
150	Intron 19	19989	A/T	rs997777
151	Intron 19	21033	G/A	
152	Intron 19	21095	A/T	
153	Intron 19	21582	G/A	rs2619313
154	Intron 19	21634	C/T	
155	Intron 19	21715	C/T	
156	Intron 19	23090	G/A	
157	Intron 19	24297	A/G	
158	Intron 19	25947	C/A	
159	Intron 19	30193	A/C	
160	Intron 19	33424	A/G	rs1189428
161	Intron 19	33474	T/C	rs1189429
162	Intron 19	34901	T/G	rs1564353
163	Intron 19	34916	G/T	rs1564354
164	Intron 19	35277	T/C	rs1564355
165	Intron 19	36938	C/G	
166	Intron 19	37322	C/T	

Table 2d. Continued

No.	Location	Position[a]	Genetic variation	NCBI SNP ID
167	Intron 19	(38361–38362)	T/ins	
168	Intron 19	38746	T/C	
169	Intron 19	41603	T/C	rs1678342
170	Intron 19	42343	C/T	
171	Intron 19	44733	A/del	
172	Intron 19	45056	T/G	rs1678394
173	Intron 20	(405–419)	$(T)_{13–15}$	
174	Intron 20	(637–648)	$(A)_{12–13}$	
175	Intron 20	842	T/del	
176	Intron 20	843	T/C	
177	Intron 20	1347	T/del	
178	Intron 20	1614	A/G	rs1729748
179	Intron 20	2222	G/A	rs1678395
180	Intron 20	4115	G/A	rs1628382
181	Intron 20	9851	T/G	rs1678363
182	Intron 20	10233	C/T	rs1729775
183	Intron 20	12141	T/G	rs1630807
184	Intron 20	12153	G/C	rs1751059
185	Intron 20	(14553–14567)	$(A)_{13–15}$	
186	Intron 20	15487	C/T	
187	Intron 20	15698	G/C	rs1678354
188	Intron 20	15951	C/A	rs1729761
189	Intron 20	16152	T/C	rs1729760
190	Intron 20	16161	T/C	
191	Intron 20	16185	A/G	rs1729759
192	Intron 20	30891	C/T	
193	Intron 20	30984	C/T	rs1189434
194	Intron 20	31180	G/A	
195	Intron 20	31283	A/del	
196	Intron 20	31526	A/G	rs1189435
197	Intron 20	32572	A/C	rs1189437
198	Intron 21	404	C/T	rs1189438
199	Intron 21	428	G/A	rs1189439
200	Intron 21	2016	C/T	rs1751052
201	Intron 21	3703	G/A	rs1678362
202	Intron 21	3898	G/C	rs1751050
203	Intron 21	3902	C/T	rs1624638
204	Intron 21	4204	A/T	
205	Intron 21	4336	T/C	rs943290
206	Intron 21	4471	C/T	rs943289
207	Intron 21	4527	A/G	rs1729755
208	Intron 21	7071	C/A	rs1751042
209	Exon 22	26	A/G(Leu904Leu)	rs1678339
210	Intron 22	1026	A/C	
211	Exon 23	38	C/T(Phe948Phe)	rs1189466
212	Intron 23	377	A/G	
213	Intron 23	395	G/A	rs1189465
214	Intron 23	602	G/A	rs1189464
215	Intron 24	99	A/G	rs2274401
216	Intron 24	1096	G/A	rs1189462
217	Intron 25	128	G/A	rs1189461
218	Intron 25	4122	C/G/T	
219	Intron 25	4422	G/C	rs1189457
220	Intron 25	4936	A/C	rs1678365
221	Intron 25	5251	A/G	rs1751036
222	Intron 25	5428	G/A	rs1678409
223	Intron 25	6418	C/A	
224	Intron 25	8764	T/C	rs1751035
225	Intron 25	(8765–8775)	$(T)_{5–11}$	
226	Exon 26	138	A/G(Lys1116Lys)	rs1751034
227	Intron 26	67	G/C	
228	Intron 26	100	T/G	rs1751033
229	Intron 26	(101–109)	$(T)_{8–9}$	
230	Intron 26	362	G/A	rs931110
231	Intron 26	463	T/C	rs922522
232	Intron 26	591	T/C	rs931111
233	Intron 26	7716	G/A	rs1189444
234	Intron 26	7816	G/A	rs1189445
235	Intron 26	7845	A/G	rs1189446
236	Intron 26	9266	A/G	rs1189449

Table 2d. Continued

No.	Location	Position[a]	Genetic variation	NCBI SNP ID
237	Intron 27	7469	G/A	rs1151471
238	Intron 28	391	T/del	
239	Intron 29	2569	C/T	
240	Intron 29	7820	C/T	
241	Intron 30	6269	A/G	
242	Intron 30	6320	C/T	
243	Intron 30	6474	A/G	
244	Intron 30	6519	C/T	
245	Intron 30	6574	C/T	
246	Intron 30	6680	A/G	
247	Intron 30	−704	A/C	
248	Intron 30	−228	A/G	
249	Intron 30	−(14–5)	$(T)_{9–10}$	
250	Exon 31	146	G/T(3′UTR)	
251	3′Flanking	173	A/G	
252	3′Flanking	(430–440)	$(A)_{10–11}$	
253	3′Flanking	556	G/A	
254	3′Flanking	741	T/C	rs1059751
255	3′Flanking	1144	T/C	
256	3′Flanking	1426	A/T	
257	3′Flanking	1454	C/T	rs1059762

ABCC4, ATP-binding cassette, subfamily C, member4

Table 2e. Summary of genetic variations detected in the *ABCC5* gene

No.	Location	Position[a]	Genetic variation	NCBI SNP ID
1	Intron 1	628	G/C	
2	Intron 1	1834	C/T	
3	Intron 1	3055	A/del	
4	Intron 2	−20280	T/C	
5	Intron 2	−20260	A/T	
6	Intron 2	−19204	C/T	
7	Intron 2	−19043	G/A	
8	Intron 2	−18824	A/G	
9	Intron 2	−18807	G/A	
10	Intron 2	−(18735–18734)	A/ins	
11	Intron 2	−16898	C/T	rs2292997
12	Intron 2	−15903	G/A	
13	Intron 2	−15901	C/T	
14	Intron 2	−15847	G/A	
15	Intron 2	−15605	C/T	
16	Intron 2	−13571	G/A	
17	Intron 2	−13402	G/T	
18	Intron 2	−13325	G/C	
19	Intron 2	−7293	C/T	
20	Intron 5	374	C/T	
21	Intron 5	1490	T/C	rs939338
22	Intron 5	(2212–2213)	CT/del	
23	Intron 5	3283	C/T	
24	Intron 5	3469	C/T	
25	Intron 5	4411	G/C	rs939337
26	Intron 5	4630	C/T	rs2313212
27	Intron 7	28	G/A	rs2293001
28	Intron 7	443	C/T	
29	Intron 7	458	T/G	
30	Exon 9	38	C/T(Ala395Ala)	rs2271938
31	Intron 9	176	A/G	
32	Intron 9	214	G/T	
33	Intron 10	703	T/C	
34	Intron 10	3580	A/G	
35	Intron 10	3655	G/A	
36	Intron 10	3854	T/C	
37	Intron 10	5040	C/T	
38	Intron 10	5062	C/T	rs869335
39	Intron 10	5316	C/T	
40	Intron 11	213	A/G	rs869417

Table 2e. Continued

No.	Location	Position[a]	Genetic variation	NCBI SNP ID
41	Exon 12	21	T/C(Cys594Cys)	rs939336
42	Intron 12	234	G/A	
43	Intron 12	300	A/G	
44	Intron 12	318	A/G	
45	Intron 12	1545	C/T	
46	Intron 13	20	T/C	
47	Intron 14	13	C/T	rs2271937
48	Intron 14	76	C/T	rs1879257
49	Intron 14	278	A/G	
50	Intron 15	117	A/C	rs2292999
51	Intron 16	(1654–1663)	$(T)_{9–10}$	
52	Intron 16	1664	A/T	
53	Intron 17	20	T/G	
54	Intron 18	232	C/T	
55	Intron 19	249	G/A	
56	Intron 20	846	G/A	
57	Intron 20	1154	A/del	
58	Intron 22	(1424–1425)	AT/ins	
59	Intron 22	1799	T/C	rs2280392
60	Intron 23	50	C/G	rs1016752
61	Intron 23	1279	G/A	rs2292998
62	Intron 24	132	A/G	
63	Intron 24	−874	A/G	
64	Intron 24	−630	G/A	
65	Intron 24	−102	G/C	
66	Exon 25	120	C/T(Leu1208Leu)	
67	Intron 26	263	C/T	
68	Intron 26	−3717	G/A	rs2037379
69	Intron 26	−3257	T/C	
70	Intron 27	873	G/A	
71	Intron 29	(2733–2734)	TGTCCAAAGGAAGGACACG/ins	
72	Intron 29	2959	A/G	
73	Intron 29	4020	G/A	
74	Exon 30	684	G/A(3′UTR)	
75	Exon 30	947	C/T(3′UTR)	
76	Exon 30	(1145–1160)	$(TC)_{6–8}$(3′UTR)	
77	Exon 30	1345	A/G(3′UTR)	rs562
78	3′Flanking	4	A/C	
79	3′Flanking	1729	C/T	rs2313217
80	3′Flanking	1911	C/T	rs1533684
81	3′Flanking	1958	A/G	rs1000002
82	3′Flanking	2008	C/del	
83	3′Flanking	2052	A/G	
84	3′Flanking	2238	G/A	rs1533683
85	3′Flanking	2845	A/G	rs1533682

ABCC5, ATP-binding cassette, subfamily C, member5

Table 2f. Summary of genetic variations detected in the *CFTR* gene

No.	Location	Position[a]	Genetic variation	NCBI SNP ID
1	5′Flanking	−834	T/G	
2	5′Flanking	−729	T/del	
3	Exon 1	125	G/C(5′UTR)	rs1800501
4	Intron 1	6200	G/A	rs2283054
5	Intron 1	7538	C/A	
6	Intron 1	9203	T/C	rs885993
7	Intron 1	13519	T/C	rs2237721
8	Intron 1	14110	T/del	
9	Intron 1	14293	C/del	
10	Intron 1	14316	C/G	
11	Intron 1	14433	G/A	
12	Intron 1	14824	G/C	
13	Intron 1	23401	C/G	
14	Intron 3	879	C/A	

Table 2f. Continued

No.	Location	Position[a]	Genetic variation	NCBI SNP ID
15	Intron 3	922	G/C	
16	Intron 3	933	C/T	
17	Intron 3	2632	A/C	rs980574
18	Intron 3	13704	A/del	
19	Intron 3	13758	A/G	
20	Intron 3	21578	G/A	rs1429566
21	Intron 4	240	T/del	
22	Intron 4	376	A/G	
23	Intron 4	586	T/C	
24	Intron 4	1089	G/A	rs957461
25	Intron 4	1101	T/A	rs213942
26	Intron 4	1615	C/T	
27	Intron 4	1946	T/C	
28	Intron 6	783	A/G	
29	Intron 6	(1104–1131)	$(GATT)_{6-7}$	
30	Intron 7	(731–732)	T/ins	
31	Intron 7	1434	T/C	
32	Intron 7	1481	A/G	rs213935
33	Intron 8	752	A/G	rs2237725
34	Intron 8	1109	G/A	
35	Intron 8	1312	T/del	
36	Intron 9	(6499–6520)	$(TG)_{11-12}$[b]	
37	Intron 10	395	G/A	rs1820871
38	Intron 10	2119	T/G	
39	Intron 10	2406	G/A	rs213946
40	Exon 11	16	G/A(Val470Met)[c]	rs213950
41	Intron 11	3867	A/del	
42	Intron 11	11844	A/del	
43	Intron 11	12144	T/C	rs2082056
44	Intron 11	20975	G/A	
45	Intron 11	21152	A/G	rs213955
46	Intron 11	21297	G/A	rs213956
47	Intron 11	27057	G/A	
48	Intron 11	27131	T/del	
49	Intron 12	1280	G/A	rs213963
50	Intron 12	1449	A/G	rs213964
51	Intron 12	1650	T/A	rs213965
52	Intron 13	152	T/A	
53	Intron 13	287	T/C	
54	Intron 14	1826	A/G	rs117243
55	Intron 15	(85–86)	AT/del	
56	Intron 15	106	T/A	
57	Intron 15	3267	T/G	rs213976
58	Intron 15	3333	T/G	rs213977
59	Intron 15	3341	A/C	
60	Intron 15	5556	A/T	rs2246450
61	Intron 15	5919	C/A	rs2106155
62	Intron 15	6282	A/T	rs2213958
63	Intron 17	2479	A/C	rs2299445
64	Intron 18	−81	A/del	
65	Intron 19	751	A/G	
66	Intron 19	820	T/C	
67	Intron 20	1011	G/T	rs213980
68	Intron 21	1532	T/del	
69	Intron 21	1607	C/T	rs2237726
70	Intron 21	4244	G/A	rs213985
71	Intron 21	11260	T/C	
72	Intron 22	(130–131)	AT/del	
73	Intron 23	1837	A/del	
74	Intron 24	(7100–7112)	$(T)_{12-14}$	
75	Intron 25	237	C/T	
76	Exon 27	115	C/T(Arg1453Trp)	
77	Exon 27	334	T/del(3′UTR)	

CFTR, Cystic fibrosis transmembrane conductance regulator
[b] SNP previously reported by Chu et al. (1993)
[c] SNP previously reported by Cuppens et al. (1998)

Table 2g. Summary of genetic variations detected in the *ABCC8* gene

No.	Location	Position[a]	Genetic variation	NCBI SNP ID
1	5′Flanking	−1099	T/C	
2	5′Flanking	−(424–422)	CAC/del	
3	Intron 1	382	G/C	rs985136
4	Intron 1	1212	A/G	
5	Exon 2	59	T/C(Pro69Pro)[b]	rs1048099
6	Intron 2	1003	C/A	rs2283253
7	Intron 2	1253	C/T	rs2283254
8	Intron 2	1382	T/C	rs2283255
9	Intron 2	2371	T/A	
10	Intron 3	1957	C/T	
11	Intron 3	(2088–2089)	CCA/ins	
12	Intron 3	2204	G/A	rs2283257
13	Intron 3	2286	A/G	
14	Intron 3	2312	C/G	
15	Intron 3	2356	A/G	
16	Intron 3	2359	A/C	
17	Intron 3	2370	G/A	
18	Intron 3	2382	A/G	
19	Intron 3	4910	G/A	
20	Intron 3	4969	A/G	
21	Intron 3	5003	C/G	
22	Intron 3	5019	A/C	
23	Intron 4	14	C/T[b]	rs2301703
24	Intron 4	187	G/A	rs2301704
25	Intron 4	204	G/C	
26	Intron 4	254	G/A	
27	Intron 4	357	G/C	
28	Intron 5	92	G/A	rs2074317
29	Intron 5	801	C/T	rs886289
30	Intron 5	802	A/G	rs886290
31	Intron 6	87	A/G	rs886291
32	Intron 6	4205	G/A	rs2237975
33	Intron 6	5519	A/C	rs2237976
34	Intron 6	5575	G/C	rs2237977
35	Intron 6	6587	C/T	rs2073585
36	Intron 6	6747	C/T	rs2073586
37	Intron 7	348	A/C	rs2057661
38	Intron 8	28	G/A	rs1800850
39	Intron 8	4015	T/G	rs886292
40	Intron 9	191	A/G	rs2073587
41	Intron 10	1963	T/G	rs2283261
42	Intron 10	2047	T/C	rs886293
43	Intron 10	2724	A/G	rs2237979
44	Intron 10	2938	G/C	rs2237980
45	Intron 10	3094	T/del	
46	Intron 10	3368	A/G	rs2237981
47	Intron 10	8897	C/T	
48	Intron 11	308	G/A	
49	Intron 11	1171	G/A	rs2074308
50	Exon 12	7	G/A(Val560Met)	
51	Exon 12	15	C/T(His562His)	rs1799857
52	Intron 12	356	G/T	
53	Intron 12	934	G/T	
54	Intron 12	1370	C/G	rs2283262
55	Exon 14	25	G/A(Lys649Lys)	rs1799858
56	Intron 15	412	C/T	
57	Intron 15	688	A/G	
58	Intron 15	709	C/T[c]	rs1799854
59	Intron 16	4464	G/A	rs2237988
60	Intron 16	4574	T/C	
61	Intron 16	5011	C/T	rs2299638
62	Intron 16	6138	A/T	rs929235
63	Intron 16	7608	C/G	rs2299641
64	Intron 16	7730	G/A	rs2299642
65	Intron 16	7818	C/G	rs916828
66	Intron 16	8369	T/C	rs2237991
67	Intron 16	9708	T/G	rs2074315
68	Intron 17	651	A/G	rs2234773
69	Intron 17	692	A/G	
70	Intron 17	1541	C/T	

Table 2g. Continued

No.	Location	Position[a]	Genetic variation	NCBI SNP ID
71	Intron 18	580	C/T	
72	Intron 18	658	C/T[b]	
73	Intron 18	660	T/C[b]	
74	Intron 19	93	T/C	
75	Intron 19	123	T/C	
76	Intron 19	219	C/T	
77	Intron 19	845	C/T	rs2074309
78	Intron 20	338	A/G	rs2355017
79	Exon 21	10	C/T(Leu829Leu)	
80	Intron 21	192	C/del	
81	Intron 23	17	A/G	rs2106865
82	Intron 23	67	C/T	
83	Intron 23	581	T/C	rs1319447
84	Intron 26	268	G/C	rs2077654
85	Intron 26	308	C/T	rs2077655
86	Intron 26	348	A/G	rs2077144
87	Intron 26	613	A/G	rs739688
88	Intron 26	807	G/A	
89	Intron 26	834	G/C	rs2073583
90	Intron 28	(118–121)	AAAA/del	
91	Intron 28	1348	G/A	rs2067043
92	Intron 29	1253	G/T	
93	Intron 29	1589	A/G	
94	Intron 29	2322	G/A	rs2074310
95	Intron 29	2348	T/C	rs2074311
96	Intron 29	2418	C/T	rs2074312
97	Intron 29	2494	C/A	
98	Intron 29	2735	C/T	
99	Intron 30	386	C/T	
100	Exon 31	66	G/A(Arg1273Arg)[c]	rs1799859
101	Exon 33	117	T/G(Ser1369Ala)	rs757110
102	Intron 33	93	G/T	
103	Intron 33	358	C/T	
104	Intron 33	446	T/C	rs757111
105	Intron 33	959	T/C[d]	rs759689
106	Intron 38	54	G/C	
107	Intron 38	466	C/del	
108	Intron 38	529	A/G	

ABCC8, ATP-binding cassette, subfamily C, member8
[b] SNPs previously reported by Nestorowicz et al. (1998)
[c] SNPs previously reported by Inoue et al. (1996)
[d] SNP previously reported by Goksel et al. (1998)

Table 2h. Summary of genetic variations detected in the *ABCC9* gene

No.	Location	Position[a]	Genetic variation	NCBI SNP ID
1	Intron 2	−321	T/C	rs870134
2	Intron 2	−266	A/G	rs870135
3	Intron 3	38	C/A	
4	Intron 3	305	T/A	rs2176394
5	Intron 3	320	A/G	
6	Intron 3	631	G/C	
7	Intron 3	8644	A/G	
8	Intron 4	757	A/C	
9	Intron 4	1022	A/C	
10	Intron 5	−1217	A/G	
11	Intron 5	−1208	A/G	rs1344569
12	Intron 5	−180	A/G	rs1517276
13	Intron 6	(100–106)	$(T)_{8-9}$	
14	Intron 6	1347	A/del	
15	Intron 6	1618	G/A	rs2418021
16	Intron 6	1835	C/T[b]	
17	Intron 7	407	T/G	
18	Intron 7	423	C/T	
19	Intron 8	743	A/T	
20	Intron 8	850	T/G	

Table 2h. Continued

No.	Location	Position[a]	Genetic variation	NCBI SNP ID
21	Intron 8	1360	C/T	rs1421602
22	Intron 9	585	A/T	
23	Intron 9	1394	G/C	
24	Intron 11	1035	A/G	rs704217
25	Intron 12	908	T/C	rs704215
26	Intron 12	1113	T/C	rs1914361
27	Intron 12	1167	G/A	rs2292771
28	Intron 12	1195	A/G	rs2292772
29	Intron 12	2123	G/A	
30	Intron 12	2622	G/A	rs704212
31	Intron 12	(2653–2656)	TAAC/del	
32	Intron 12	2756	G/A	rs2032775
33	Intron 13	(3043–3044)	CTCTTT/ins or CT/ins	
34	Intron 13	4877	A/C	rs1283802
35	Intron 13	4887	A/G	rs1356368
36	Intron 14	85	T/A	
37	Intron 14	275	T/C	
38	Intron 14	453	T/C	
39	Intron 14	3709	G/A	
40	Intron 14	3813	C/T	
41	Intron 14	4000	A/del	
42	Intron 14	5522	T/A	rs1492138
43	Intron 14	5535	T/G	rs704205
44	Intron 16	1466	A/C	
45	Intron 16	5357	T/G	
46	Intron 16	7395	A/G	rs697252
47	Intron 16	7407	C/T	rs768314
48	Intron 17	970	A/T	rs704194
49	Intron 17	(1358–1368)	$(T)_{10–11}$	
50	Intron 18	119	C/T	rs704193
51	Intron 18	773	T/C	rs704192
52	Intron 18	865	A/G	rs704191
53	Intron 20	98	G/A	
54	Intron 20	173	C/T	rs704189
55	Intron 22	28	A/C	rs2307024
56	Intron 22	194	G/del	
57	Intron 22	1370	C/T	
58	Intron 22	1487	C/G	
59	Intron 22	3148	T/G	rs1283822
60	Intron 23	(455–462)	AATTAGAA/del	
61	Intron 23	1221	A/G	rs829080
62	Intron 23	1976	C/A	rs829079
63	Intron 24	(460–465)	TTTAAAA/TTTTAA	
64	Intron 24	595	A/G	rs2307025
65	Intron 26	−150	T/G	rs1643235
66	Intron 27	1628	C/T	rs704179
67	Intron 27	1770	C/G	rs704178
68	Intron 27	1976	A/T	rs704177
69	Intron 28	−926	G/A	rs2112080
70	Intron 29	667	T/C	rs1283811
71	Intron 29	1072	A/C	rs1283810
72	Intron 29	2692	T/del	
73	Intron 29	2959	T/C	rs1873638
74	Intron 29	5464	G/A	
75	Intron 29	−1830	A/T	
76	Intron 31	102	G/A	rs2638441
77	Intron 33	877	A/G	
78	Intron 33	1069	T/C	rs2216525
79	Intron 36	(1270–1281)	$(T)_{11–12}$	
80	Intron 37	533	C/G	rs829060
81	3′Flanking	197	T/G	

ABCC9, ATP-binding cassette, subfamily C, member9

[b] SNP previously reported by Iwasa et al. (2001)

Table 3. Summary of genetic variations in eight *ABCC* genes

Gene	All genetic variations	SNPs	Insertion/deletion polymorphisms	Novel	Total base pairs sequenced (kb)	Frequency (bp/1SNP)
ABCC1	95	81	14	53	37.7	465
ABCC2	41	41	0	28	38.0	927
ABCC3	35	30	5	19	26.4	880
ABCC4	257	230	27	156	97.7	425
ABCC5	85	76	9	63	39.6	521
CFTR	77	58	19	47	79.4	1369
ABCC8	108	102	6	49	50.0	490
ABCC9	81	70	11	39	53.9	770
Total	779	688	91	454	422.7	(average) 614

Table 4. Number and region of SNPs detected in eight *ABCC* genes

				Exon				
					Coding			
Gene	5′Flanking	Intron	3′Flanking	5′UTR	Nonsynonymous	Synonymous	3′UTR	Total
ABCC1	1	67	3	0	1	6	3	81
ABCC2	0	34	1	1	2	3	0	41
ABCC3	1	25	1	0	0	3	0	30
ABCC4	2	211	6	1	3	6	1	230
ABCC5	0	63	7	0	0	3	3	76
CFTR	1	54	0	1	2	0	0	58
ABCC8	1	94	0	0	2	5	0	102
ABCC9	0	69	1	0	0	0	0	70
Total	6	617	19	3	10	26	7	688

Table 5. Novel SNPs detected in exons in seven *ABCC* genes

Region	Gene	Location	Position	SNP
5′UTR	*ABCC4*	Exon 1	67	C/T
Coding				
Nonsynonymous	*ABCC1*	Exon 18	53	G/A(Arg723Gln)
	ABCC2	Exon 28	52	A/C(Lys1299Gln)
	ABCC4	Exon 4	205	T/G(Cys171Gly)
		Exon 18	56	G/A(Glu757Lys)
	CFTR	Exon 27	115	C/T(Arg1453Trp)
	ABCC8	Exon 12	7	G/A(Val560Met)
Synonymous	*ABCC1*	Exon 25	60	G/A(Pro1150Pro)
	ABCC2	Exon 22	51	G/A(Ser978Ser)
		Exon 28	84	C/T(Tyr1309Tyr)
		Exon 28	129	C/T(Ile1324Ile)
	ABCC3	Exon 22	180	C/T(Gly1013Gly)
	ABCC5	Exon 25	120	C/T(Leu1208Leu)
	ABCC8	Exon 21	10	C/T(Leu829Leu)
3′UTR	*ABCC1*	Exon 32	652	C/T
	ABCC4	Exon 31	146	G/T
	ABCC5	Exon 30	684	G/A
		Exon 30	947	C/T

Table 6. Genetic variations identified in the upstream region of the splice acceptor site

Gene	Location	Position	Genetic variation	Flanking sequence[a]
ABCC1	Intron 13	11824	A/G	tcctaggatgatgactctcactc a/g gggcacagcagtcagcactgggcgttctgcttgcagGTGGC
	Intron 19	(3369–3374)	$(CA)_{2-3}$	ccaagctaggcagtct $(ca)_{2-3}$ tgtgcact g/c acgtggccgggtgtccccttgcccacagACGCG
	Intron 19	3383	G/C	
	Intron 22	(4428–4445)	$(GGGGCT)_{3-4}$	$(ggggct)_{3-4}$ gggtgcgtgcatgtgctaagctgccttatctcctgtgatctccagGTCAA
	Intron 29	1920	G/A	tccatccatgtcagc g/a tgacacaggtgtcacatgccgtccactctcttctctctgaacagGACCC
	Intron 30	(1708–1714)	$(T)_{6-7}$	gttcagggtcagggtggtttgacccaacactatctcctgg $(t)_{6-7}$ cttccggtcaagTGTCG
ABCC3	Intron 5	206	G/A	tctgctttgagagggtggtgggcactcctgattccccc g/a tcctattctctcgccttctagAACCC
	Intron 7	1537	C/T	ttggcttcctggagcccctgtccccattcctaaccacctgct c/t cttcctccctggaccagACACA
	Intron 12	85	C/del	tgcccaggcatggccagggctcattggactctaccctga c/del accacctccacgctgctcagGTGAC
	Intron 18	303	G/A	gcctgtgccagggtgtgctggagggtggtag g/a ggtgagagcctgctgccttctccccagACGCG
ABCC4	Intron 2	543	T/C	cccctgttttatattgtggcagggttcactcttatttacgaagcttttcctcat t/c gtagGTTCT
	Intron 6	1474	G/A	ccgctgataagggcaggctgtgatc g/a ctcaggctcatctcccgtgtctggttcccctagGAGTA
	Intron 25	8764	T/C	gctgcatcctgtgatttttttt t/c $(t)_{5-11}$ aatcctgccgcctggatctctctgtagGTTGG
	Intron 25	(8765–8775)	$(T)_{5-11}$	
	Intron 30	−(14–5)	$(T)_{9-10}$	cagggaggagactttaaaattttgaaacattcttttatgcttacc $(t)_{9-10}$ ctagGTATA
ABCC5	Intron 16	(1654–1663)	$(T)_{9-10}$	tgtggacattcatctggatggctaacatgactggagac $(t)_{9-10}$ a/t aatattattagATCAA
	Intron 16	1664	A/T	
CFTR	Intron 6	(1104–1131)	$(GATT)_{6-7}$	agataatttgacttgtttttactatta $(gatt)_{6-7}$ tacagAGATC
	Intron 9	(6499–6520)	$(TG)_{11-12}$	ctgacaaactcatctttattttttga $(tg)_{11-12}$ ttttttttaacagGGATT
ABCC8	Intron 15	688	A/G	ggtaatggttgttcagactccccggccccactcac a/g tctgccaccttccctccctg c/t agGCCAG
	Intron 15	709	C/T	
	Intron 18	658	C/T	ctgagaacaagccccctgagaatgc c/t t t/c ccgcaccccctactcccgccctgctttttccagGAAGA
	Intron 18	660	T/C	
	Intron 33	959	T/C	tagaggctattcccagcagccccagagtcccag t/c ggcggtgcctgcttctctctttccagATCGG
	Intron 38	529	A/G	tgccccccaccgcgggtggt a/g ttcccaccatcctgacccgcccccctcctgccctgcccagCATCG
ABCC9	Intron 4	1022	A/C	ttttaatatgtggaaaataattggactaattgttatactgtggaatttttcttgc a/c acagAGATA
	Intron 17	(1358–1368)	$(T)_{10-11}$	atacacgcacagtacctttgcataatcctggtg $(t)_{10-11}$ ctttttcatttttcagTAGCA
	Intron 36	(1270–1281)	$(T)_{11-12}$	ggcaaaatattatgatgacaaagtaatcccgagaaaatttacac $(t)_{11-12}$ gcagGAGAA

[a] Capital letters indicate exonic sequences and lowercase letters correspond to intronic sequences. Double-underlined and underlined sequences indicate putative branch-point sequences. Double-underlined sequences completely match to the branch-point consensus sequence. Underlined sequences match 6 of 7 nucleotides corresponding to the branch-point consensus sequence

Table 7. SNPs identified in the downstream region of the splice donor site

Gene	Location	Position	Genetic variation	Flanking sequence[a]
ABCC1	Intron 10	8	A/G	GGAAGgtagggg a/g cgctgtgccattggcatgtggc
	Intron 31	18	G/A	ACAAGgtgatgccactggcaca g/a tggcctctaggc
ABCC3	Intron 20	29	C/T	ATGAGgtgagttcctgagagctcccagccctcc c/t g
ABCC5	Intron 7	28	G/A	CAATGgtgagtaagcctcccagctgaatcctg g/a ca
	Intron 13	20	T/C	GAAAGgcaaggaatgtttggcttc t/c gtcatgcttt
	Intron 14	13	C/T	CGGAGgtacaggccttc c/t gcccctgaccaggcatt
	Intron 17	20	T/G	GGAAGgtaatggccttttttgaaa t/g ttttagattt
ABCC8	Intron 4	14	C/T	TGAGGgtaagcaggccac c/t tgggccagggtggggt
	Intron 8	28	G/A	TACAGgtactagatgggctgaggggaagggag g/a gg
	Intron 23	17	A/G	AGAAGgtgggtatatccaggg a/g tggccaagcagcc
ABCC9	Intron 22	28	A/C	AAAAGgtaagtgctcatagttcagaagagttc a/c ga

[a] Capital letters indicate exonic sequences and lowercase letters correspond to intronic sequences

TG repeat would place the branchpoint A nucleotide of the lariat in a less favorable position for splicing. Hence, some of these polymorphisms found near the exon–intron junctions might influence posttranscriptional processing of the transcripts.

In conclusion, these genetic variations should contribute to studies that investigate possible correlations of genotypes with disease-susceptibility phenotypes, and responsiveness or adverse effects to drugs. All data for the genetic variations reported here are available through our website (http://snp.ims.u-tokyo.ac.jp/).

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