

Aritoshi Iida · Susumu Saito · Akihiro Sekine
Yukie Kataoka · Wataru Tabei · Yusuke Nakamura

Catalog of 300 SNPs in 23 genes encoding G-protein coupled receptors

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Abstract We previously published a series of detailed maps of single nucleotide polymorphisms (SNPs) in the genomic regions of 209 gene loci encoding drug metabolizing enzymes, transporters, receptors, and other potential drug targets. In addition to the maps reported earlier, we provide here high-resolution SNP maps of 23 genes encoding G-protein coupled receptors in the Japanese population. A total of 300 SNPs were identified through screening of these loci; 83 in four adenosine receptor family genes, 45 in three adrenergic receptor family genes, 22 in three EDG receptor family genes, 29 in three melanocortin receptor family genes, 22 in two somatostatin receptor family genes, 21 in five anonymous G protein-coupled receptor family genes, and 78 in the others (*AVPR1B*, *OXTR*, and *TNFRSF1A*). We also discovered a total of 33 genetic variations of other types. Of the 300 SNPs, 132 (44%) appeared to be novel on the basis of comparisons with the dbSNP database of the National Center for Biotechnology Information (US) or with previous publications. The maps constructed in this study will serve as an additional resource for studies of complex genetic diseases and drug-response phenotypes

to be mapped by linkage-disequilibrium association analyses.

Keywords Single nucleotide polymorphism · Adenosine receptor genes · Adrenergic receptor genes · EDG receptor genes · Melanocortin receptor genes · Somatostatin receptor genes · Anonymous G protein-coupled receptor genes · Japanese population · High-density SNP map

Introduction

One of major goals in our laboratory is to establish “personalized medicine” on the basis of single nucleotide polymorphisms (SNPs) regarding responsiveness or adverse effects to drugs and susceptibility to common diseases. To achieve this aim, we have been conducting extensive screening programs to isolate SNPs in the Japanese population. Particularly, we have focused on SNP mapping in 209 genomic regions that correspond to genes involved in the metabolism of drugs and have constructed high-density SNP maps containing more than 6,500 genetic variations (Iida et al. 2001a,b,c,d,e, 2002a,b,c,d, 2003; Saito et al. 2001a,b, 2002a,b,c,d, 2003a,b; Sekine et al. 2001). Moreover, these efforts have allowed us to identify a total of five mutations that may affect the gene products, including two nonsense mutations in *CYP* genes and three frame-shift mutations (two in *CYP* genes and one in the *MGST1* gene) among Japanese healthy donors (see a review by Iida and Nakamura 2003).

G-protein coupled receptors are cell-surface proteins and are responsible for the signal transduction for a variety of extracellular chemical signals such as photons, Ca^{2+} , nucleotides, amino acids, peptides, amines, fatty derivatives, and various polypeptide ligands (see a review by Howard et al. 2001). On recognition of such ligands, these proteins mediate a variety of intracellular signals via activation of heterotrimeric G-proteins that in turn, activate various effector proteins, consequently

A. Iida (✉) · Y. Nakamura
Laboratory for Pharmacogenetics, Research Groups
of Personalized Medicine, RIKEN SNP Research Center,
c/o RIKEN Yokohama Institute, 1-7-22 Suenhiro-cho,
Tsurumi, Yokohama, Kanagawa 230-0045, Japan
E-mail: iidaari@src.riken.go.jp
Tel.: +81-45-5039599
Fax: +81-45-5039326

S. Saito
Laboratory for SNP Analysis, Research Groups
of Personalized Medicine, RIKEN SNP Research Center,
c/o Institute of Medical Science, The University of Tokyo,
Tokyo, Japan

A. Sekine · Y. Kataoka · W. Tabei
Laboratory for Genotyping, RIKEN SNP Research Center,
c/o RIKEN Yokohama Institute, Kanagawa, Japan

Y. Nakamura
Laboratory of Molecular Medicine, Human Genome Center,
Institute of Medical Science, The University of Tokyo,
Tokyo, Japan

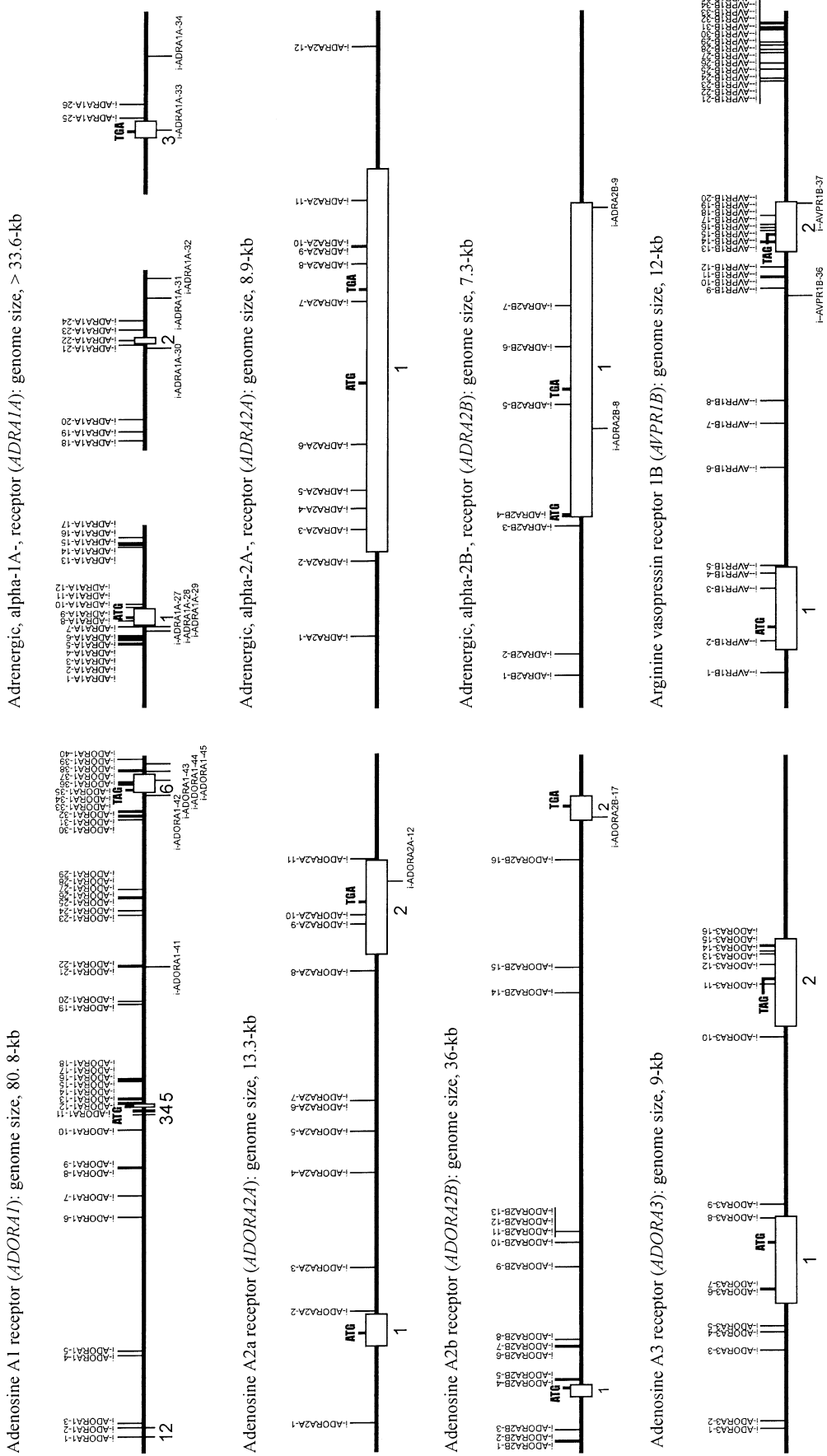


Fig. 1 Fine-scale single nucleotide polymorphism (SNP) maps of 23 gene loci encoding G-protein coupled receptors. Exons and introns are represented by *rectangles* and *horizontal lines*, respectively. SNPs are indicated *above* the lines (designations correspond to the left-most column of Table 1). Genetic variations of other types, where present, are indicated *below* the maps. However, the complete 5' untranslated sequences and/or 3' untranslated sequences of *ADRA2B*, *EDG5*, *MC3R*, *MC4R*, *SSTR3*, *GPR3*, and *GPR10* were yet unidentified in database we used

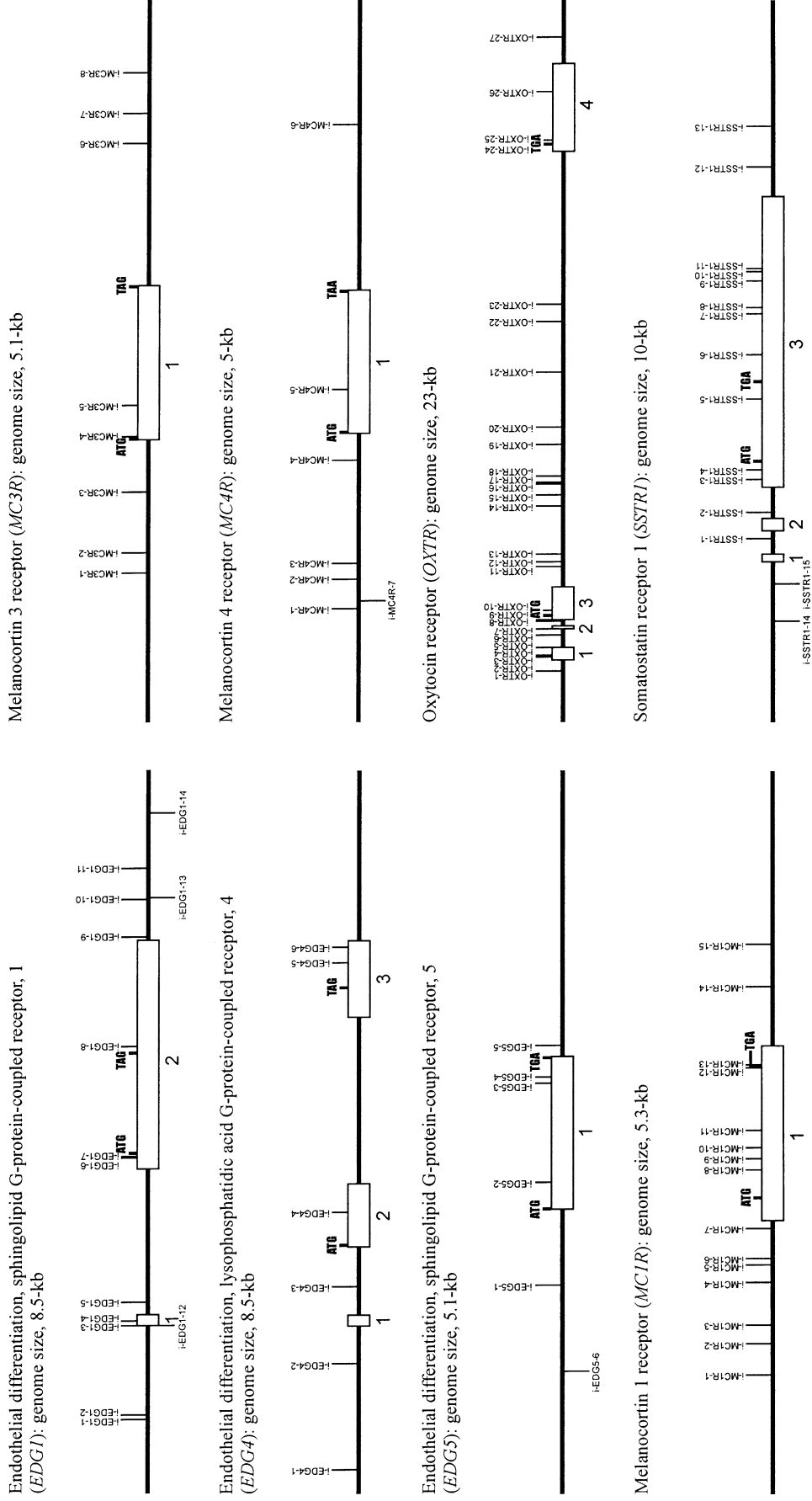


Fig. 1 (continued)

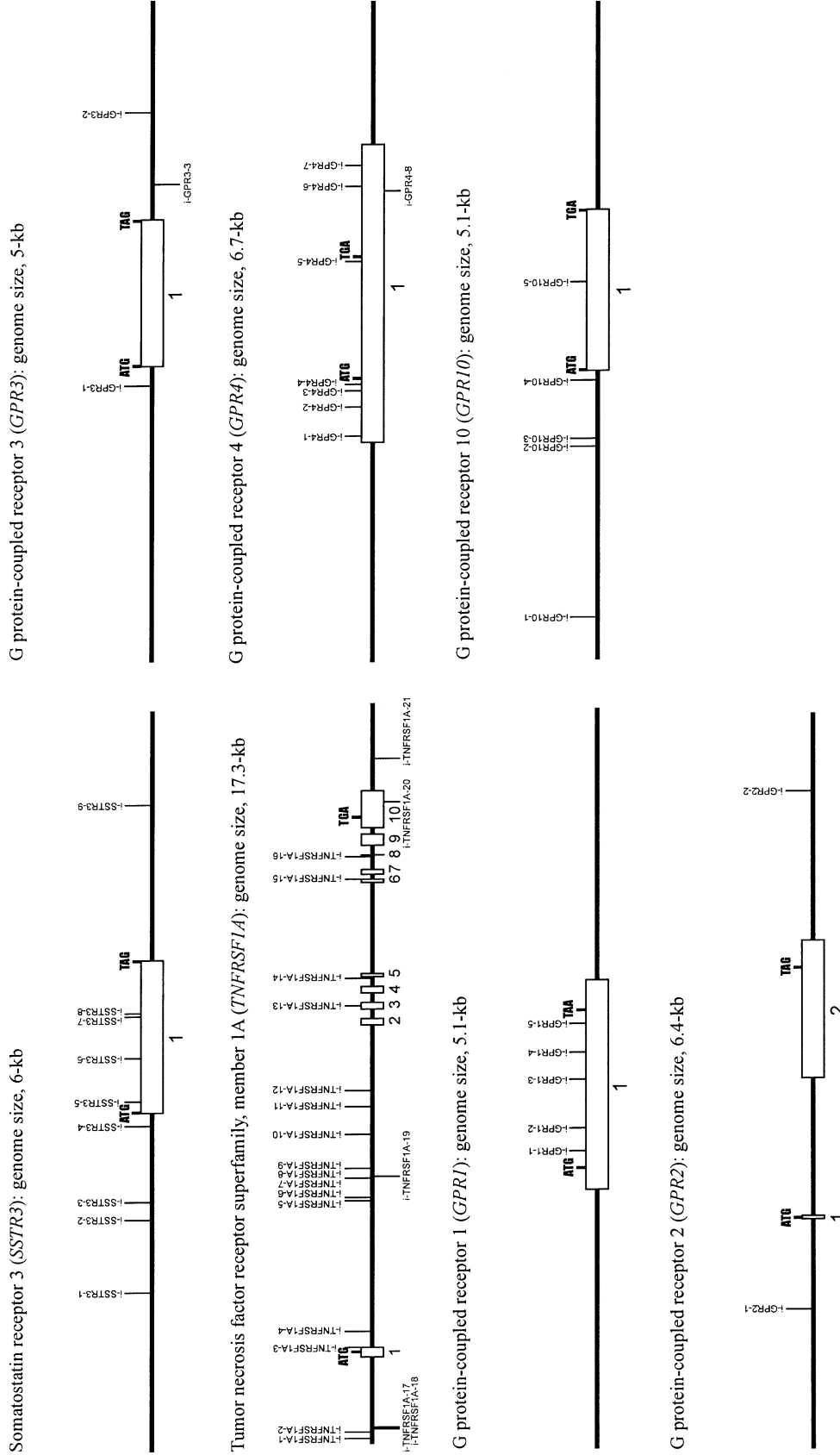


Fig. 1 (continued)

Table 1 Summary of genetic variations identified in 23 gene-encoding G-protein coupled receptors. *SNP* Single nucleotide polymorphism

Gene symbol	Accession number (genomic DNA)	Genome size	Screening region	SNP	Other type of variation	Total	Nonsynonymous substitution	Identity to dbSNP/ previous report	New SNP
<i>ADORA1</i>	AC105940.2	80.8	22.9	40	5	45	0	20	20
<i>ADORA2A</i>	AP000355.1	13.3	9.1	11	1	12	1	7	4
<i>ADORA2B</i>	AC006251.3	36	11.9	16	1	17	0	10	6
<i>ADORA3</i>	AL390195.10	9	6.3	16	0	16	1	10	6
<i>ADRA1A</i>	AC025712.4	> 33.6	18.4	26	8	34	1	18	8
<i>ADRA2A</i>	AL158163.11	8.9	8.4	12	0	12	0	10	2
<i>ADRA2B</i>	AC092603.2	7.3	5.2	7	2	9	0	4	3
<i>AVPR1B</i>	AF152238.1	12	8	35	2	37	3	1	34
<i>EDG1</i>	AL109741.19	8.5	6.6	11	3	14	0	6	5
<i>EDG4</i>	AC011458.7	8.5	4.5	6	0	6	0	3	3
<i>EDG5</i>	AC011511.12	5.1	3.3	5	1	6	1	4	1
<i>MC1R</i>	AC092143.3	5.3	4.7	15	0	15	4	11	4
<i>MC3R</i>	AL139824.22	5.1	3.5	8	0	8	2	7	1
<i>MC4R</i>	AC091576.11	5	4.8	6	1	7	1	3	3
<i>OXTR</i>	AF176315.2	23	14.5	27	0	27	1	17	10
<i>SSTR1</i>	AL450109.3	10	8.5	13	2	15	0	7	6
<i>SSTR3</i>	Z82188.2	6	4.9	9	0	9	0	7	2
<i>TNFRSF1A</i>	AC006057.5	17.3	10.7	16	5	21	1	11	5
<i>GPR1</i>	AC007383.4	5.1	2.4	5	0	5	3	4	1
<i>GPR2</i>	AC027146.1	6.4	3.7	2	0	2	0	1	1
<i>GPR3</i>	AL096774.9	5	4	2	1	3	0	1	1
<i>GPR4</i>	AC011480.3	6.7	3.2	7	1	8	0	3	4
<i>GPR10</i>	AC067895.2	5.1	4.9	5	0	5	0	3	2
Total		289.4	174.4	300	33	333	19	168	132

resulting in a physiologic response for the cell (Marinissen and Gutkind 2001). G-protein coupled receptors are members of a large multigene family characterized by similar structure, which consists of seven alpha-helical transmembrane segments connected by three intracellular and three extracellular loops, an extracellular amino-terminal domain, and an intracellular carboxyl-terminal domain. So far, a large number of studies have reported genetic variations of G-protein coupled receptor gene loci and their role in etiology or predisposition of human diseases (Rana et al. 2001). G-protein coupled receptors are also considered to be good potential targets for drug development (Howard et al. 2001).

To expand the genetic basis for drug development as well as eventually to enable clinicians to predict efficacy and adverse drug reactions, we explored SNPs among 23 genes encoding G-protein coupled receptors. In this report, we provide high-resolution maps of these gene loci containing a total of 300 SNPs and 33 genetic variations of other types that we detected in DNAs from 48 Japanese volunteers.

Subjects and methods

Samples of peripheral blood were obtained with written informed consent form 48 healthy Japanese volunteers for this study. The SNP screening method described in an earlier report by Haga et al. (2002) was the principal technique applied in this study. In brief, on the basis of genomic sequences corresponding to each of the receptor genes from the GenBank database in the US National Center for Biotechnology Information (NCBI), we designed primers to amplify all selected genes in their entirety, excluding only regions that corresponded to repetitive sequences predicted by

the RepeatMasker program (<http://repeatmasker.genome.washington.edu/cgi-bin/RepeatMasker>). All gene symbols mentioned through this report are according to the nomenclature in LocusLink of NCBI.

Each polymerase chain reaction (PCR) was performed using 20 ng of a mixture of genomic DNAs from three individuals. All 16 mixed samples were amplified in the GeneAmp PCR system 9700 (PE Applied Biosystems, Foster City, Calif., USA) under the following conditions: initial denaturation at 94°C for 2 min, followed by 35 cycles of denaturation at 94°C for 30 s, annealing at 60°C for 30 s, extension at 72°C for 2 min, and post-extension at 72°C for 7 min. Products obtained from the PCR experiments served as templates for direct sequencing and detection of SNPs, using the fluorescent dye-terminator cycle-sequencing method. All SNPs detected by the polyphred computer program (Nickerson et al. 1997) were confirmed by sequencing both strands of each PCR product.

Results and discussion

By direct sequencing of DNA from 96 chromosomes, we screened SNPs in a total of approximately 174.4-kb genomic sequences that accounted for 60% of the 289.4-kb genomic region encompassing the loci of 23 selected genes, excluding the regions corresponding to human repetitive sequences. We identified a total of 333 variations, including 300 SNPs and 33 genetic variations of other types, and constructed a fine-scale SNP map of each locus (Fig. 1, Table 1). Detailed information for each variation identified in this study is summarized in Table 2. The overall genomic distribution of SNP was 1 in every 581 nucleotides in the 174.4-kb region that we sequenced. The overall frequencies of nucleotide substitutions in our test population were counted as 31% for A/G, 36.3% for C/T, 10% for C/G, 9.3% for T/G, 7.3%

Table 2 Characterization of 333 genetic variations in 23 gene loci corresponding to G-protein coupled receptors. *dbSNP* Database of single-nucleotide polymorphisms, *ins* insertion polymorphism, *del* deletion polymorphism

ID	Location	Exon	Position ^a	5' Flanking sequence ^b	Variation ^c	3' Flanking sequence ^b	Substitution	Identity to dbSNP/ previous report
Adenosine A1 receptor								
i-ADORA1-1	5' Flanking region		-54	gtccacctctctccaccaca	C/T	atggggaaatggaggccccag		rs7518889
i-ADORA1-2	Intron 2		79	tgtcactactactgttgat	T/G	tgccccctggctgtccct		
i-ADORA1-3	Intron 2		533	tctcttcaactgtggcttc	G/A	titttctattctaaagfgc		rs1389793
i-ADORA1-4	Intron 2		8422	tagggcaggggtgggtgga	C/A	ttgtctccagggcacaagga		
i-ADORA1-5	Intron 2		8904	gtttgtttgtttgttt	T/C	aaattctgaacctagagcc		
i-ADORA1-6	Intron 2		24377	ctggggcaagggaacaag	G/C	ctgtctctccaggagataa		rs729215
i-ADORA1-7	Intron 2		26819	caactactactcttacc	C/T	gacctgaggaaagtgcactt		
i-ADORA1-8	Intron 2		30037	aaataagatcaactttgct	C/T	ctcagtccccagccactat		rs7555556
i-ADORA1-9	Intron 2		30138	tctcttagtttaactttt	C/T	gtcaictttgaccatgattg		
i-ADORA1-10	Intron 2		34431	ccaagctgaagatgctgic	A/C	atagttagacaaggfagacc		
i-ADORA1-11	Coding region	5	306	ctggcccgtctggcaattgc	T/G	gtggaccgtactccgggt	Ala102Ala	rs2228079
i-ADORA1-12	Intron 5		145	tccagtcctactctgctt	T/C	ccgtgctccgtctgcagggg		
i-ADORA1-13	Intron 5		508	aggcagcgtttggctcttc	A/G	ttcaccagggtatctctgic		
i-ADORA1-14	Intron 5		567	aggcctttccagctgaacc	A/G	acagctgatttaactttgcc		
i-ADORA1-15	Intron 5		2547	aagcaaggatccctggcag	G/C	tgttggggcattctggggct		
i-ADORA1-16	Intron 5		2719	gcccagatgccatcaaa	G/A	gtatagttggccctggggcac		rs3766568
i-ADORA1-17	Intron 5		2763	gagctgactgacccagcac	T/A	gttggggcgtgctgggggca		
i-ADORA1-18	Intron 5		2922	taataigtaccagttacaaa	T/A	tftttcttttaagctcaa		rs1494485
i-ADORA1-19	Intron 5		11491	ggtgctctccactccag	C/T	tgctctcttccaccttact		
i-ADORA1-20	Intron 5		11942	ggcatcaccaggtctcagat	C/T	tagccagccctgattggcag		rs3753476
i-ADORA1-21	Intron 5		15950	caggagaagccccaccccc	C/G	accagacttaaaccaatag		rs3753475
i-ADORA1-22	Intron 5		16109	gggtgaggtgaaagtga tcccc	C/T	aatictgcccgcacaaggsgga		rs3753474
i-ADORA1-23	Intron 5		21833	tctaggtcccaaccaccgc	G/T	ggfctcttgggctgctatc		rs1845466
i-ADORA1-24	Intron 5		22340	ttgtatctctcaaggctc	G/A	attggtattccagtagaat		rs3766558
i-ADORA1-25	Intron 5		23766	gactggggagaaaaggatgag	G/C	ttaagaaggcaaatatacttt		rs3766557
i-ADORA1-26	Intron 5		24059	gctctcacactgggggat	C/A	cccttgcctcaggtgctgggc		
i-ADORA1-27	Intron 5		24806	aga gtaggggaacggaaag	G/A	gaagattcaatcccctgacta		
i-ADORA1-28	Intron 5		24870	gaegtggacctctgccacc	C/G	cegcccctccacctccctgc		
i-ADORA1-29	Intron 5		24948	gaacagggcagcccaagcc	T/C	gaggaccctgctctggcttc		rs6677137
i-ADORA1-30	Intron 5		32975	ttcccacgtgtaaggatag	G/A	tgagcttctctctggcctt		rs3753473
i-ADORA1-31	Intron 5		33223	agaagaagggaaggaccac	T/C	tctgtagctagaagtctct		rs3753472
i-ADORA1-32	Intron 5		33471	atttcaacctggccaatcat	C/T	tgcattctcaacaaccacag		
i-ADORA1-33	Intron 5		33734	tcctctctgagtgagct	C/T	gctttccctgctgaggttca		rs3766556
i-ADORA1-34	Intron 5		33997	tcagagatactggagtttt	C/T	caggtggccatttctctggg		rs3766555
i-ADORA1-35	3' UTR	6	1278	ccatcccatgacagaccag	C/A	gcttcaaggctgggcagctc		
i-ADORA1-36	3' UTR	6	1405	ttaga gttggfsgcagc	C/T	ccaaggacaagcttaaggag		rs6427994
i-ADORA1-37	3' UTR	6	1627	ggggcagccagagattgfac	G/T	tgggagagcagaaaagggtg		
i-ADORA1-38	3' Flanking region		384	ggcccctcccagatgatgt	C/T	gctcacitggcacagggccc		
i-ADORA1-39	3' Flanking region		451	tttagtgcctcccaccag	T/A	gtgcaactcccagggcact		rs1042295
i-ADORA1-40	3' Flanking region		15885-15886	tcccagtgcttgaatggtgga	C/T	ggccggaggattctctagcc		
i-ADORA1-41	Intron 5		35829-35830	aggagttgattcafgcca	CA/ins	gtcaaggctggaagaaa		
i-ADORA1-42	Intron 5		1795	aggagctcctctgatttt	T/ins	ctattattttttgcat		
i-ADORA1-43	3' UTR	6	350-351	agcttccggggaaggacct	T/del	ggagtgtaattacctgcat		
i-ADORA1-44	3' Flanking region		1254-1255	aaacattcagataccccccc	C/ins	tccctgtagacacagccctc		
i-ADORA1-45	3' Flanking region			cacagctctcccctgact	C/T/ins	tcagtgccggctgaggctg		

Table 2 (Continued)

ID	Location	Exon	Position ^a	5' Flanking sequence ^b	Variation ^c	3' Flanking sequence ^b	Substitution	Identity to dbSNP/ previous report
Adenosine A2a receptor								
i-ADORA2A-1	5' Flanking region		-1470	ggcagtggtggtggcgctggc	A/C	acacactataggcccccat		rs7288656
i-ADORA2A-2	Intron 1		64	ccaggcttggctcgtgccc	G/A	gagccagggtgagcctggga		
i-ADORA2A-3	Intron 1		891	ttggggccctgagcccatg	C/T	atgaggcttgggtggctg		rs2267076
i-ADORA2A-4	Intron 1		2674	ctctccataactttttt	T/A	aaaaaaaagaactcagtttt		
i-ADORA2A-5	Intron 1		3460	ccccgaaaaggcgagcctg	C/T	aagccgggggacacagagct		
i-ADORA2A-6	Intron 1		4028	ggagactctttgcaagta	C/T	ggfagaagactccccctg		rs8184997
i-ADORA2A-7	Intron 1		4056	gactccccctgfggtfccc	T/G	ttctgtaacaagtaacaat		rs4822489
i-ADORA2A-8	Intron 1		6518	agagaaaaatcagtfttcc	C/T	cccaaaaaatcagcgtta		rs2236625
i-ADORA2A-9	Coding region	2	899	cgagftccgcagacctfcc	G/A	caagatcattccagccacg	Arg300His	rs4990
i-ADORA2A-10	Coding region	2	1083	gagcgaaggccaatgacta	T/C	gccctgggctggfagtag	Tyr361Tyr	rs5751876
i-ADORA2A-11	3' Flanking region		27	cgctgagttggttctctac	T/A	ccatagctaggccctfgcac		
i-ADORA2A-12	3' UTR	2	1696-1697	aggtgacattfgacttttt	T/ins	ccaggaaaaatgtaagtg		
Adenosine A2b receptor								
i-ADORA2B-1	5' Flanking region		-2304	acaggaaaatgctagaagcaga	G/T	cccaggccccagcgtgcag		
i-ADORA2B-2	5' Flanking region		-2252	accactcatagcaacagcc	A/G	gacaccgftcgcctctctc		
i-ADORA2B-3	5' Flanking region		-1696	tccctgtaatcatccaccc	G/A	gctagaggtgtactcgtg		rs2779193
i-ADORA2B-4	Intron 1		224	gfcctctaaggagatcgc	G/T	tagggacagctctaaagggt		
i-ADORA2B-5	Intron 1		249	gagactctataggggtccgg	G/A	gagtgccgtcccccggccc		
i-ADORA2B-6	Intron 1		1967	agaaactcgaagctcggccc	A/G	tctgcttctctggcccgtc		rs758855
i-ADORA2B-7	Intron 1		2045	ccccagctcccgccccagag	G/T	tagtctctgacctggccac		rs758856
i-ADORA2B-8	Intron 1		2299	cttiaaccagggacattggg	T/G	tccagcattcnaagatcct		rs758858
i-ADORA2B-9	Intron 1		6050	taggcagggggcaaggctcg	G/A	tttggfcafgfagfctctca		rs2535607
i-ADORA2B-10	Intron 1		7299	ctctctaaattttaactc	C/G	ataggctcttggactccgag		rs2535609
i-ADORA2B-11	Intron 1		7843	ccccacaagctctcggcc	A/G	ggggcagccccagcctggt		rs2779199
i-ADORA2B-12	Intron 1		7881	gtttctctggcatttgccc	T/C	ggggggc(T/G)ctctgggctgag		rs2535610
i-ADORA2B-13	Intron 1		7889	tgccattggccc(T/C)gagggg	T/G	ctctgggctgagcccctggt		
i-ADORA2B-14	Intron 1		20174	caagtcgcactcccgtagaa	A/G	ggccatccttagccctgctgg		rs2779207
i-ADORA2B-15	Intron 1		21504	gfgggcccgaggaggagac	T/A	ggcctggggagagagacag		rs2779211
i-ADORA2B-16	Intron 1		27038	egctccattctctgccc	A/G	taactactgtcactaagc		
i-ADORA2B-17	Coding region	2	(454-456) or 457-459	gtaaagacagtgccacc(aac)	AAC/del	tgcaagaaacctggagagg	(152) or 153Asn/del	
Adenosine A3 receptor								
i-ADORA3-1	5' Flanking region		-1622	gocctgagccaccagtagga	G/A	gctgcaagcattcctactftg		
i-ADORA3-2	5' Flanking region		-1521	aggaatggggcaaatgagatg	A/G	cctcttggccccagcctctct		rs2298191
i-ADORA3-3	5' Flanking region		-602	gtctcccttatgcccacac	C/T	gaagfittttagtaaaca		
i-ADORA3-4	5' Flanking region		-377	caagtggtgtcccaataac	A/T	atggcggtgcaaggtctggt		
i-ADORA3-5	5' Flanking region		-283	agacagtcctctctctcc	G/T	gggaaggccgagggcttgg		
i-ADORA3-6	5' UTR	1	-581	gctgcagaaagattgca	A/G	tcagtgctccaagctc(T)gct		rs1544223
i-ADORA3-7	5' UTR	1	-564	ata(A/G)tcagctccagctc	C/T	gctcccactgatctctgac		rs1544224
i-ADORA3-8	Coding region	1	322	tgtggccatcgtctggac	C/T	gatacttggcggfcaagctt	Arg108Stop	
i-ADORA3-9	Intron 1		164	ttgtctgtagggggttagca	T/A	caatggctctggactcaagg		
i-ADORA3-10	Intron 1		2299	ttagctggaatcaccatag	G/A	tatcaatgctggcctctctt		rs2798566
i-ADORA3-11	Coding region	2	897	taccttttgatcctcaaac	C/T	tgtgtgcttggcctccc	Ala299Ala	rs2229155
i-ADORA3-12	3' UTR	2	1146	ttctccactcattttcc	T/C	ttgctcttctcttaattc		rs923
i-ADORA3-13	3' UTR	2	1293	gacttactgacaaaagctc	T/C	agttgggctgaaatgctg		rs1415793
i-ADORA3-14	3' UTR	2	1334	tggtgtgactcatttccat	G/A	ccatttgggaattgagcaga		rs1415792
i-ADORA3-15	3' UTR	2	1380	tgcctcggaggaagcttag	A/G	agatgttgggaaacaagaa(G)aa		rs3393
i-ADORA3-16	3' UTR	2	1398	ag(A/G)agatgttgggacagaa	G/A	aaataaacaggtttaagggg		rs3394

Gene/Region	Position	Sequence	Reference	
Adrenergic, alpha-1A ⁺ , receptor	i-ADRA1A-1	5' Flanking region	rs1075764	
	i-ADRA1A-2	5' Flanking region	rs3808585	
	i-ADRA1A-3	5' Flanking region	rs737045	
	i-ADRA1A-4	5' Flanking region	rs486179	
	i-ADRA1A-5	5' Flanking region	rs573542	
	i-ADRA1A-6	5' Flanking region	rs574584	
	i-ADRA1A-7	5' Flanking region	rs1383914	
	i-ADRA1A-8	5' UTR	rs3824230	
	i-ADRA1A-9	Intron 1	rs528257	
	i-ADRA1A-10	Intron 1	rs573514	
	i-ADRA1A-11	Intron 1		
	i-ADRA1A-12	Intron 1		
	i-ADRA1A-13	Intron 1		
	i-ADRA1A-14	Intron 1	rs538378	
	i-ADRA1A-15	Intron 1	rs489790	
	i-ADRA1A-16	Intron 1	rs536401	
	i-ADRA1A-17	Intron 1		
	i-ADRA1A-18	Intron 1		
	i-ADRA1A-19	Intron 1		
	i-ADRA1A-20	Intron 1		
	i-ADRA1A-21	Intron 1		
	i-ADRA1A-22	Coding region		
	i-ADRA1A-23	Intron 2		
	i-ADRA1A-24	Intron 2		
	i-ADRA1A-25	3' Flanking region		
	i-ADRA1A-26	3' Flanking region		
	i-ADRA1A-27	5' Flanking region		
	i-ADRA1A-28	5' Flanking region		
	i-ADRA1A-29	5' Flanking region		
Adrenergic, alpha-2A ⁺ , receptor	i-ADRA1A-30	Intron 1		
	i-ADRA1A-31	Intron 2		
	i-ADRA1A-32	Intron 2		
	i-ADRA1A-33	3' UTR		
	i-ADRA1A-34	3' Flanking region		
	i-ADRA2A-1	5' Flanking region		
	i-ADRA2A-2	5' Flanking region		
	i-ADRA2A-3	5' UTR		
	i-ADRA2A-4	5' UTR		
	i-ADRA2A-5	5' UTR		
	i-ADRA2A-6	5' UTR		
	i-ADRA2A-7	Coding region		
	i-ADRA2A-8	3' UTR		
	i-ADRA2A-9	3' UTR		
	i-ADRA2A-10	3' UTR		
	i-ADRA2A-11	3' UTR		
	i-ADRA2A-12	3' Flanking region		
	<p>caatccccgcgcgagcgtg ccccctatccccccccgga gagtcctccgcgtaaggttcg cttgcgaagctccctctgca tggacagacctgggctgctt tgaagcgtctcgtggctcgtg tgaaggttaactggcggccagc gggagggtggccctggacagc cttcggttacccccagactcc aaalgcactcgtc(T/C)ctcta ctctagctctcagagctccca catttctactgctacaga atatactatcattatatt attcttaaatatgacgtgct aggggatgagtgctatccca tccactaaagcctgggtgct aaaagagaaaggaagataaga gggggatgtggcccaagcaca agctgtctctcgggttttaa attcggagagaacaagtfga tggagaaactcatalgtgctg gcaaaaagcagctctccaaa tactgacagccacattgac ggctctgcatcacaaga ctaaagggtgctcttccca gtttgttttcgcttggat (GATG/del)ccatcggctcccttgg ccatcggctccctgcttfga aacaattacatattggac tatctaaaattgtgcagtt tgcgaaactggatatacccaa ttttttttttatcttttt gggggatctcctgccaactat cttttgattctgaaattagg tgaaggatgctgtgtataca ggagggagccctggcgcgca caticgaagcccgccctcc gagctgcacagcccaatccc ggagctccgcacagtggtccc ggcagaaccgcgagaaagc caccttgacctggagccat aagaaaaatgctaaagggcag ctgctcgttttttagactcca gctcgttttttagactcca agccccagaccacaggctg</p>			
	<p>G/A G/A C/T G/A A/G A/G G/A C/A G/T T/A T/C C/T A/C C/T C/T C/T A/G C/T C/T T/C T/C G/C A/T T/C T/ins ACCTGTAGGC- TGGCTACCCAA/ins GATG/del TTTTCAAATTAGGCAA/del A/ins TTTCTTTTTCACAA/ins T/del G/del C/T T/A G/T C/T G/C C/G C/A C/A A/G C/A G/A A/G</p>			
	<p>ccgggaccgaagccgggtcc ttccacaggtttataccg ctcacccgcgtctctgc caaatccgcagtgactgic tgaaggcttggaaagcgtic cgaattccaccggcgtgaga cttcggctggccgagctcaaa ctccgcctccggccagcc tggggcttcaccctctcg ctataagcacggttcaatt caatt(T/A)aatgcatcigtctc ctiaggctgactgtggaatg aaaatfgtagcagaagaata tattatattcaagggacata attaaaaactgaaaccaagg ttccctttcccaagctctc gggtcagccctcaacctac tggccctgagccctgctcctt gctctaaactttagctcta ctccatcaatgacacct tcttgaagaatccagctcic atitttttcaagctcaac atagagactagtcagtcmeta aaagaaatggaagaccca gggaaatgggctctgaaagtg tttggggattgttttttt cgggccagggagcagggcca ggggcagagcagggcca (ACCTGTAGCGCTG- CGTACCCAA/ins) tactttcaatttaggcaa cctttaaagcaagcaaaaa gtgacatcgttgttcttaa caccgtgcccgcccaacta tggccatccacatgaaggca taaatgttttttatttcc tctactcccttcccetta tggcagaagacttaagagac tccattccgccccaggggtt gcttctcctccgtcggccc cccgcgcgcgcgcgctccc aggcgtcgcgcgtggcggg atcccagftgtgttttgg ccaactctctctctttt agaaaaatgctaaagggcagc tgaactatggggaaactttt cagacaacagcctgctggg</p>			
	<p>-1554 -1385 -1136 -993 -877 -743 -108 -50 52 307 322 370 4850 4885 4978 5128 5395 -7161 -6406 -5614 -135 1039 549 1241 126 557 -479 to -478 -76 to -75 -75 to -72 -335 to -334 2933-2934 4318-4319 1567 2321 -1083 -125 -1808 -1536 -1297 -727 1093 1569 1780 1802 2372 1569</p>			
	<p>Arg347Cys Arg365Arg</p>			

Table 2 (Continued)

ID	Location	Exon	Position ^a	5' Flanking sequence ^b	Variation ^c	3' Flanking sequence ^b	Substitution	Identity to dbSNP/ previous report
Adrenergic, alpha-2B-, receptor								
i-ADRA2B-1	5' Flanking region		-1661	gtggctgtgaataaagaggc	C/A	tggctgaggcggggccttat		
i-ADRA2B-2	5' Flanking region		-1447	ttccactgicacccccagaa	G/A	ggcttcaagtgtgtaigfegg		rs3111873
i-ADRA2B-3	5' Flanking region		-98	ccaagccctcggcggccgc	G/C	ggaggggcagcctctctgctt		
i-ADRA2B-4	Coding region	1	36	ccctactccgfgcagggccac	A/G	ggggccataagcggcggccat	Thr36Thr	
i-ADRA2B-5	Coding region	1	1173	ttctcagctcagccctggg	A/C	ggccattgcccgaaggaactg	Gly391Gly	rs2229169
i-ADRA2B-6	3' UTR	1	1767	tttttcactccccccacc	C/A	acaaagagccacggagccagc		rs4907299
i-ADRA2B-7	3' UTR	1	2194	agctctgtggggagacacac	T/G	agaagaaaccaaaatgtgatt		rs3813662
i-ADRA2B-8 ^d	Coding region	1	903-911	gatgagctgtagagaggga	AGAGGAGGA/del	ggaggagggagagagagctg		Small et al. (2001)
i-ADRA2B-9	3' UTR	1	3223-3224	gtgggtgtttttttttttt	T/ins	aaactctgagcctattttatc		
Arginine vasopressin receptor 1B								
i-AVPR1B-1	5' Flanking region		-388	accggctagccggctggcag	A/G	ggggccgcccaacagccgccca		
i-AVPR1B-2	5' UTR	1	-356	ccaagaanaagttggagaag	A/T	gaaattgaggcggattggag		
i-AVPR1B-3	Coding region	1	571	tggactgcgggagactctc	G/C	ggctccctggggggccaccgg	Gly191Arg	
i-AVPR1B-4	Coding region	1	821	cagcatcaaacaccactctac	G/A	ggccaagatcccgacacagfga	Arg274Gln	
i-AVPR1B-5	Intron 1		25	gtgggggtctctgtgggggca	G/T	tgaagtgaggagagacagaaa		rs3883899
i-AVPR1B-6	Intron 1		1721	caaggccacaattcccaca	G/C	tggctcccctcttctgtatt		
i-AVPR1B-7	Intron 1		2475	ttcccnaagggtatcttta	C/T	agacaaatgctcccagaaa		
i-AVPR1B-8	Intron 1		2847	ttctaaalgaaggaaactcg	T/C	ggaaactcttctccctggc		
i-AVPR1B-9	Intron 1		4769	gfatgtaaaaagctgcccct	T/C	ggctgttagggggcaatfgatg		
i-AVPR1B-10	Intron 1		4966	tfgaatccatgatataa	T/C	gtaagtggggatggagatgg		
i-AVPR1B-11	Intron 1		4987	gfaagtggggatggagatgg	G/A	cggggcttgagccttgggtat		
i-AVPR1B-12	Intron 1		5156	cttctatataaactggag	G/C	aaactcagctcctacccttc		
i-AVPR1B-13	Coding region	2	1091	gggtcccagcccagatgc	G/A	ccggggcctctccagcgcca	Arg364His	
i-AVPR1B-14	Coding region	2	1119	ctctccagcggcagcccttc	G/A	agcggccacaccacgcctgc	Ser373Ser	
i-AVPR1B-15	3' UTR	2	1284	atcatcttttaggaaagact	C/G	(G/A)ctggggctctggtaactgccc		
i-AVPR1B-16	3' UTR	2	1285	tcactcttaggaaagact(CG)	G/A	ctggggctctggtaactgccc		
i-AVPR1B-17	3' UTR	2	1336	ggagggtctctgccaccctc	G/A	ggcactggaaatgagagctg		
i-AVPR1B-18	3' UTR	2	1393	ggattagaggagccctgct	A/G	aaagc(G/A)gagcgaagaggccag		
i-AVPR1B-19	3' UTR	2	1398	agaaggagccctgct(A/G)aaagc	G/A	ggagcgaagaggccagaaatgg		
i-AVPR1B-20	3' UTR	2	1563	fgtccatgacacatggf	T/A	cccagagatctaggcaaggcc		
i-AVPR1B-21	3' Flanking region		2101	ccctattgtctcccaatgg	A/G	aaagctacacttgaatctttt		
i-AVPR1B-22	3' Flanking region		2145	gaaagctggttctgctctgt	G/A	atatggacagfggggagcga		
i-AVPR1B-23	3' Flanking region		2303	agctggggccaggtggaaagg	C/G	cttgggatagggttcaaggag		
i-AVPR1B-24	3' Flanking region		2393	tccacttctgacggcctaac	C/G	ccaaggagaactgaaacatg		
i-AVPR1B-25	3' Flanking region		2415	caaggagaactgaaacatg	C/T	gctctggcctggggcctgt		
i-AVPR1B-26	3' Flanking region		2595	agaatggtatgtgtttgg	C/T	acagccagtaacttcccag		
i-AVPR1B-27	3' Flanking region		2650	ttttgtatgtaaalagatca	C/T	ttactactacaaggctata		
i-AVPR1B-28	3' Flanking region		2717	ttctggggcagaaacccag	G/C	ttgaaattcacaataaaaa		
i-AVPR1B-29	3' Flanking region		2762	taataccaaggaaattctcg	C/T	ggatcttttagtttctagggg		
i-AVPR1B-30	3' Flanking region		2966	ggccctggcctccctcgggc	T/C	tgacttggcagctccctgct		
i-AVPR1B-31	3' Flanking region		2997	gctctggcctaaagaatcag	G/T	taaggcccttctctagcca		
i-AVPR1B-32	3' Flanking region		3024	cccttctctgccaatatt	G/A	ctgagatccagt(G/T)caattc		
i-AVPR1B-33	3' Flanking region		3037	aaatatt(G/A)ctgagatccagt	G/T	caacttcttaactctctcg		
i-AVPR1B-34	3' Flanking region		3078	gagatataagagcagtaatg	A/T	ctaacagggaaaggctaggaa		
i-AVPR1B-35	3' Flanking region		3111	gctaaggaaagcaccagcc	T/A	cttagctgtgagctctcaa		
i-AVPR1B-36	Intron 1		4643	tggcaatccacattttgac	T/del	ggccaagagagaaatagtt		
i-AVPR1B-37	3' UTR	2	1744-1769	tctattggatcctggatt	(GTT)8-9	agaagagaaatgcttcatg		

Gene	Region	Position	Sequence	SNP	Alleles	Reference
Endothelial differentiation, sphingolipid G-protein-coupled receptor, 1	i-EDG1-1	5' Flanking region	ctcagccctcagcttcttaag	T/C		
	i-EDG1-2	5' Flanking region	aaagctgctagtaatgagatt	T/C		
	i-EDG1-3	5' Flanking region	gagagagggagccccgcactc	C/G		rs4987248
	i-EDG1-4	5' UTR	cgcaagtcagcggggagcagc	A/G	a(G/del)taagtttgcgagagcact	rs3765684
	i-EDG1-5	Intron 1	ctactaaggagccactctcg	A/G	tcagatgtctcttgggacact	rs3753194
	i-EDG1-6	5' UTR	ctcgcctctagcgtctgc	T/C	ggagtagcgcaccocccggct	rs3737578
	i-EDG1-7	5' UTR	cggctctctcggggacacagg	G/T	ttggcacctcggggcccacc	rs3737577
	i-EDG1-8	3' UTR	tgcaagccagaggaggaag	G/A	gggagaatacgaacagcctcg	rs3765683
	i-EDG1-9	3' Flanking region	tattgagctatcactggat	T/C	gggtatgctcttgggaatcaa	
	i-EDG1-10	3' Flanking region	atiaaatcatggtttttt	T/G	tttttttt(T/ins)caggacact	
	i-EDG1-11	3' Flanking region	ggacacagttgggacataaa	G/A	ataaacctcactaataagag	
	i-EDG1-12	3' Flanking region	gggagggagccccgactc(C/G)a	G/del	taagtttgcgagagcactac	
	i-EDG1-13	3' Flanking region	tgttttttt(T/G)tttttttt	T/ins	caaggacactgcttggccttc	
	i-EDG1-14	3' Flanking region	gaagtaagaatgagaaaaa	A/del	tcttaagtaataatattgtttg	
Endothelial differentiation, lysophosphatidic acid G-protein-coupled receptor 4	i-EDG4-1	5' Flanking region	gaagaagcccaattgtgaa	C/G	acggaccatataatccctac	rs880090
	i-EDG4-2	5' Flanking region	tggcaaaagccgaaagctgggc	G/A	ggggctccggcggtgggagc	
	i-EDG4-3	Intron 1	cgcagggttctagcaagtgga	C/T	ctacaccttctgtgcaacag	rs873870
	i-EDG4-4	Coding region	caaccagatgfatggccgt	G/A	cagctgcacagccocctgcc	Val136Val
	i-EDG4-5	3' UTR	ctggttcctgctgctgtgatg	C/G	tgaagggttttaaggttgggga	
	i-EDG4-6	3' UTR	ccaggagactggccttcccc	G/A	ataagaattgaaagcagctccac	rs1054685
Endothelial differentiation, sphingolipid G-protein-coupled receptor 5	i-EDG5-1	5' Flanking region	gtgccagcactcaccagcct	G/T	ggcaacagaggggagactcca	rs8102623
	i-EDG5-2	Coding region	gggtctcattgctgggtgccc	G/A	aaacagacaagttccactcgg	rs3745268
	i-EDG5-3	Coding region	tacacgttggcagccgggga	C/T	cttgcggggaggtgcttgg	
	i-EDG5-4	Coding region	tccggcctgctcagctctgg	A/C	ggccgggggggggggggcaaa	rs2116942
	i-EDG5-5	3' Flanking region	gggttgaccacagatagagac	G/T	tggggctacttgaagccagatg	rs2116941
	i-EDG5-6	5' Flanking region	tgtctctgggtagggtggg	C/del	aagggtttctgggaaagtccaca	
Melanocortin 1 receptor	i-MC1R-1	5' Flanking region	agtggtgccaaggccctc	C/T	ccaccgtccctgctgggctt	rs3212354
	i-MC1R-2	5' Flanking region	agggctccctgaaagactcac	C/T	aggggtgccccccagccgctcc	rs3212357
	i-MC1R-3	5' Flanking region	agagtgctctcaggctctac	G/A	agatgcccgaanaacacaaac	rs3212358
	i-MC1R-4	5' Flanking region	ggcaggtcccggggagagctc	C/T	ggactctctagagggggcggcc	
	i-MC1R-5	5' Flanking region	caagccctctgttggcaagg	T/C	ggcccatgggtgggtgctcac	rs3212359
	i-MC1R-6	5' Flanking region	ccggcatgtggccgacctca	A/G	tgggaagggtctctgagaaacg	rs3212361
	i-MC1R-7	5' Flanking region	aatccctgagcccaaggcgtt	T/A	gatgccaaggaggtgcttggga	rs3212363
	i-MC1R-8	Coding region	ggccaccatgcccagaagacc	G/A	gaacctgcaactcaacctatg	Sturm et al. (2001)
Melanocortin 3 receptor	i-MC3R-9	Coding region	tgctgggtgagcggggagcaac	G/A	tgctggagagcggccgtcacc	rs2228479
	i-MC3R-10	Coding region	gcaagcagcttggacatgtca	T/C	tgacgtgatacaacctgagct	Val192Met
	i-MC3R-11	Coding region	gaaccctgcccggggcgggc	A/G	agccgttggggccatctgggg	Ile120Thr
	i-MC3R-12	Coding region	acgtcaagaggaggtgtgac	A/G	tgtctctgttgaagcgggttg	Gln163Arg
	i-MC3R-13	3' UTR	ctggtgagcggcggctcacgc	G/A	gctttaagctgtgctggggcag	Thr314Thr
	i-MC3R-14	3' Flanking region	gcaaggagccccctatgtggt	A/G	tggggctgagccccctctgag	
	i-MC3R-15	3' Flanking region	ctccccagggtgaggaagcca	C/T	agccccaagggcccccaaatg	rs3212371
	i-MC3R-1	5' Flanking region	gaagtaaaagcataaggct	C/G	cttctccaggaactttgac	Schaln-Jantti et al. (2003)
	i-MC3R-2	5' Flanking region	gagttcggggagagccctgaga	T/C	agtggtctgttcttggctca	Schaln-Jantti et al. (2003)
	i-MC3R-3	5' Flanking region	gtcttgcctgaaagaagct	T/G	taactgtagcagccgggtggc	rs6127698

Table 2 (Continued)

ID	Location	Exon	Position ^a	5' Flanking sequence ^b	Variation ^c	3' Flanking sequence ^b	Substitution	Identity to dbSNP/ previous report
i-MC3R-4	Coding region	1	17	tggaatgagcaccacaaaga	C/A	gtatctggaggagatttg	Thy6Lys	rs3746619
i-MC3R-5	Coding region	1	241	agcttcacaaagccggag	G/A	ttttcgtctctgggaatc	Val8Ile	rs3827103
i-MC3R-6	3' Flanking region		1006	gfgtgaacttcttggtagcc	C/T	ttgttttgcctatagtaac		
i-MC3R-7	3' Flanking region		1211	ggctgactagtgtcgcgaat	G/C	tcagatccctttctgcccac		rs2870730
i-MC3R-8	3' Flanking region		1504	atctgggactctcgcaca	C/G	ggccatgggtatgfttccacg		rs6014650
Melanocortin 4 receptor								
i-MC4R-1	5' Flanking region		-1207	gattttgctgggtcaactta	C/T	gatacgttaaaactctggagg		
i-MC4R-2	5' Flanking region		-1005	ggatatttagcttataaaat	C/T	aaacccctttgaaccctac		rs8087522
i-MC4R-3	5' Flanking region		-896	ctgttttccaggatttttaa	C/T	tgaaccactactgctgggt		Lubrano-
i-MC4R-4	5' Flanking region		-178	tgatgattagagtgctacct	A/C	aaagagactaaaactccat		Bertheliet al. (2003)
i-MC4R-5	Coding region	1	307	caaatggatcagaacacatt	G/A	tcataccacctataaacagt	Val103Ile	rs2229616
i-MC4R-6	3' Flanking region		1151	gattgcatgcaataaactag	C/G	ctfccacagccactcttga		
i-MC4R-7	5' Flanking region		-1157 to -1156	agttgctataaaaaaaaaa	A/ins	cagaaatgcagcttattttt		
Oxytocin receptor								
i-OXTR-1	5' Flanking region		-353	taaaactaccgaaaaaataa	C/A	gcctct(C/T)ccagcactgctta		rs1465386
i-OXTR-2	5' Flanking region		-346	accgaaaaataa(C/A)gcctct	C/T	ccagcactgcttgaataaga		rs3806675
i-OXTR-3 ^e	5' UTR	1	-550	tcctgcgcgtggcctcggc	C/T	gccccctagcggaccgctg		rs2301260
i-OXTR-4	5' UTR	1	-485	acaagccgcctaccagcgc	T/C	gtccgcgcgcagccctggg		rs968389
i-OXTR-5	Intron 1		21	gtagctggtgctaaagcag	G/A	gtagcagggatgagctagg		rs2301261
i-OXTR-6	Intron 1		397	tcctagaaaaagggttaga	C/T	ggggaaaggaccagcctggg		
i-OXTR-7	Intron 1		606	agattccactccggaggga	A/G	cgttgcctgatttgaacctc		rs237915
i-OXTR-8	Intron 2		132	ccggctcggaaagaaacgc	G/T	ggcgtctctcaccggccctc		rs237913
i-OXTR-9	5' UTR	3	-135	cggttgtttcaagggtggac	T/C	cagcagatccctccgfggag		rs237911
i-OXTR-10	Coding region	3	171	ctctgggcctggagcgggaa	C/T	gctgtgctgctgctggcct	Asn57Asn	rs2228485
i-OXTR-11	Intron 3		667	gaggtgactactgcaaggag	T/C	gggtggcaggcttatggagg		rs237897
i-OXTR-12	Intron 3		811	ggggaattgctctccaggt	A/T	gggggactgctgaggaccag		rs2268496
i-OXTR-13	Intron 3		1088	tgcctggtggatgattta	T/C	aaagtgttttggaggccaa		
i-OXTR-14	Intron 3		2638	cagttagaacaccagccgtg	T/C	gctccactggccttaattg		rs237893
i-OXTR-15	Intron 3		3002	tgggacacatgggtctgt	C/T	ccctgttatacagaaacc		rs151463
i-OXTR-16	Intron 3		3350	caggcagtagggagaagaaa	A/G	ggaaaaaaacttatacaat		rs53576
i-OXTR-17	Intron 3		3396	taataatactattaataa	G/A	tagctctctgtatagac		rs2268494
i-OXTR-18	Intron 3		3586	gacttggtagagcctggtag	A/C	ctggatgccccatgcaaggct		rs2268491
i-OXTR-19	Intron 3		4581	tgtttctgggactgtagga	T/C	ccctgggcatgtcccgtaca		
i-OXTR-20	Intron 3		5157	ctggggtagagctctggtccc	C/T	gggctggcctgctgggigt		
i-OXTR-21	Intron 3		6906	gccaagctgacatgcata	A/T	atgtgggacacccgtggctcaa		
i-OXTR-22	Intron 3		8554	ttaactctgtagcccccc	G/A	tttggctctcaccagacc		
i-OXTR-23	Intron 3		9108	ctctggctccaccctcca	T/G	gaaatcattggcccaataga		
i-OXTR-24	Coding region	4	1126	ccctcttggctggaccat	C/G	gcaactccaccagaggagc	Arg376Gly	rs1042778
i-OXTR-25	3' UTR	4	1288	ctatacattgttatccctcc	C/A	ctcctggggtggctcagf		
i-OXTR-26	3' UTR	4	2817	tcaagaagggtgaaagaataa	C/A	ctgcagaaaggaggaaataa		
i-OXTR-27	3' Flanking region		866	tgaactctggggtgcaaatg	A/C	gcaagctgggggtctgttag		
Somatostatin receptor 1								
i-SSTR1-1	Intron 1		226	agccttattaaagagattg	G/A	aatggttcaictcaggtccct		rs4073844
i-SSTR1-2	Intron 2		98	tggactggcggatcgggagag	A/G	agctggggctctccagagaa		rs4394988
i-SSTR1-3	5' UTR	3	-239	tcctcctctctctccac	G/A	gtccctctgctccggcacc		
i-SSTR1-4	5' UTR	3	-103	cccggagggcctggaggcctg	T/G	ggggctgcaaggcaagcctg		

i-SSTR1-5	Coding region	3	879	tctacgtgtgacagctggt	C/T	aacgtgtttgtgacgagga	Val293Val	rs2228497	
i-SSTR1-6	3' UTR	3	1486	gacctcctctatttccc	T/C	accctgcaacttctatcctt			
i-SSTR1-7	3' UTR	3	2054	cctactgcgcgttttcaa	G/A	gaccaagcgcctggcgcctcc			
i-SSTR1-8	3' UTR	3	2146	cccgggttcgggttcggg	G/A	ttcgtttgacaggctgcagc		rs1135473	
i-SSTR1-9	3' UTR	3	2519	ttcttggacctggggggcg	G/A	gcatggagaagtgagggg		rs1135474	
i-SSTR1-10	3' UTR	3	2632	ccctagctttctattttt	G/C	attgtgtgagtgaagtftg		rs4143959	
i-SSTR1-11	3' UTR	3	2675	gattttcatcttttctta	C/T	tatagctcttfttfttctt		rs4640088	
i-SSTR1-12	3' Flanking region	425		ataacctgaggaagaacaac	G/A	agaaggsgaanaactatctct			
i-SSTR1-13	3' Flanking region	993		taaacaaatagcaaacatc	C/T	agftgagctgataatataa			
i-SSTR1-14	5' Flanking region	-823		tcagccgatgaaattcaaa	A/del	ttccatcttagacatctct			
i-SSTR1-15	5' Flanking region	-297 to -288		agftgcatggagtgatttc	TTCCTTCCAC/del	aggaacaagttggaaagccaa			
Somatostatin receptor 3									
i-SSTR3-1	5' Flanking region	-1463		tgggcaggggtgaccaggc	G/A	tgctcagaggcgtttftttg			
i-SSTR3-2	5' Flanking region	-867		aagacctggagtgcggggg	G/C	gctcttgccttatgtgcaaa			
i-SSTR3-3	5' Flanking region	-725		aaacccaaccggcctctggg	G/T	agaaggsgcctcagccacct		rs6000607	
i-SSTR3-4	5' Flanking region	-108		fgtcagcagtcocccaggtt	T/C	ggcatgatggagggggcag		rs69264	
i-SSTR3-5	Coding region	99		accttggcaacgtgtcggc	G/A	ggcccaagcccgcagaggct	Ala99Ala	rs86583	
i-SSTR3-6	Coding region	1	453	fggtacatcccaccgcctc	A/G	ggccgtggcgcacagctcc	Ser151Ser	rs229569	
i-SSTR3-7	Coding region	1	792	atggtggtggcgttggggc	A/G	ctcttgcgtcgtcgtggat	Ala264Ala	rs2071710	
i-SSTR3-8	Coding region	1	822	ctctgctggatgcccttca	C/T	fgctcaacatcgtcaact	Tyr274Tyr	rs5756556	
i-SSTR3-9	3' Flanking region	1280		gtggacaagccaggggtgcaa	C/T	ggcaaatgcacagatcacag			
Tumor necrosis factor receptor superfamily, member 1A									
i-TNFRSF1A-1	5' Flanking region	-1931		tgatgggtggagctgcttc	C/T	tttctgaatccagcttcaac			
i-TNFRSF1A-2	5' Flanking region	-1786		ggcaggaagaccaggggac	G/A	fgtgcacttggggctgggagg		rs767455	
i-TNFRSF1A-3	5' Flanking region	36		fgcctgacctgctgctgcc	A/G	ctggtagaccagggacaata	Pro12Pro	rs4149623	
i-TNFRSF1A-4	Intron 1	364		agfeggagtagaaattag	T/C	ggcggggagctccagagcgt		rs4149577	
i-TNFRSF1A-5	Intron 1	3420		cccaggaatgcggagaggac	C/T	ggagatcacagggggagggc		rs4149578	
i-TNFRSF1A-6	Intron 1	3505		tggggccctggggagagagc	G/A	tggcaagttctcagcttccg		rs4149580	
i-TNFRSF1A-7	Intron 1	3952		tggaggctcgttctgggag	C/T	tggag(A/G)ggacacaggggag		rs4149581	
i-TNFRSF1A-8	Intron 1	3957		gtctgttctggag(C/T)gag	A/G	ggacacaggggagggatag		rs1860545	
i-TNFRSF1A-9	Intron 1	4165		ggggggaggaacaacacat	C/T	gtcaatggfggcttccaggg		rs887477	
i-TNFRSF1A-10	Intron 1	4960		gggttgcctctgctgggac	T/G	ggggagtgcttggggatggg		rs2284344	
i-TNFRSF1A-11	Intron 1	5613		ttaaaggctgctggggctgg	C/G	gtcccccagttcttccat			
i-TNFRSF1A-12	Intron 1	5979		cagcgtctcccctggctga	C/G	tcagggtgacttgccctctg	Thr90Ile	rs1800692	
i-TNFRSF1A-13	Coding region	3	269	gttggagcggctctctca	C/T	cgttcagaaaacacctca		rs1800693	
i-TNFRSF1A-14	Intron 4	187		ggggfgggggtgacagcgt	T/C	ctccttttagctgcccac			
i-TNFRSF1A-15	Intron 6	10		tgagactcaggtgagagga	A/G	fgaacctggfcccctgctc			
i-TNFRSF1A-16	Intron 7	294		tttatgatcttcttctt	T/C	ttcctcagtttggggaat			
i-TNFRSF1A-17	5' Flanking region	-1707 to -1702		aagttccaagcccctagagc	CTCCCT/del	cttctctcttgcctgcaat			
i-TNFRSF1A-18	5' Flanking region	-1663 to -1662		ttctagcagctcagcagct	AGAAATTTCTAGC-TGCCTGCATTTCT-AGCAGCCCA/ins	ggaggcccttgggggggct			
i-TNFRSF1A-19	Intron 1	4002-4003		ttctgaccaagacattttt	T/ins	gatctctcatcttataaggt	Glu13Glu	rs3755227	
i-TNFRSF1A-20	3' UTR	1741-1745		ttttttttttttttttttt	T/TTTT/del	aaatacaatcattgttaacta	Phe65Leu	rs1060384	
i-TNFRSF1A-21	3' Flanking region	768-769		ctcttctatactacacccc	CC/ins	accaccatacagacatcccc	Asp177Asp	rs3732082	
G protein-coupled receptor 1									
i-GPRI-1	Coding region	1	39	acattatttgaagaattga	A/G	aactatcctatgaocitaga			
i-GPRI-2	Coding region	1	193	tcgactttgttcaacgggg	T/C	tcaagfggagaagacagctc			
i-GPRI-3	Coding region	1	531	ccctgcctgacttccggga	C/T	actctggagttcctaataca			
i-GPRI-4	Coding region	1	706	tcacttaaggtgaaagaag	C/T	gaaagctcctgactcctcagt	Arg236Stop		
i-GPRI-5	Coding region	1	919	accctcatcctttatgctca	A/G	tttagtaagaaagttccaaagt	Ile307Val	rs3732083	

Table 2 (Continued)

ID	Location	Exon	Position ^a	5' Flanking sequence ^b	Variation ^c	3' Flanking sequence ^b	Substitution	Identity to dbSNP/ previous report
G protein-coupled receptor 2								
i-GPR2-1	5' Flanking region		-786	gttcttgctccctctt	G/C	tctctatctctctctt		rs3809757
i-GPR2-2	3' Flanking region		1294	gcgccgcgggaggccg	G/A	ccccccccggcgctagc		
G protein-coupled receptor 3								
i-GPR3-1	5' Flanking region		-125	tgggataaggcattggag	T/C	ctatcaggatctctgaggag		rs2504786
i-GPR3-2	3' Flanking region		724	ggttttattttttaaga	A/C	gccatcacctgagcaacaa		
i-GPR3-3	3' Flanking region		229-238	ctactcaaaatgctca	GCCCAGCTGG/del	gtfgcaattccaagaatgctg		
G protein-coupled receptor 4								
i-GPR4-1	5' UTR	1	-527	gccagcactcccaccat	T/C	gccigaactttccaacactc		rs3745818
i-GPR4-2	5' UTR	1	-277	gftgacacactgactccata	C/T	ataacctcttgaaaaactc		
i-GPR4-3	5' UTR	1	-127	ccctctcttccctgtaga	C/T	ccatcccaccatgttcccc		rs3745819
i-GPR4-4	5' UTR	1	-60	ggccccatggccctcccctc	C/T	ctfgggccccacagccccg		
i-GPR4-5	Coding region	1	1044	tggcggccatctcccccctc	C/T	caaggggaccacagtgacagct	Ser348Ser	
i-GPR4-6	3' UTR	1	1720	tcigtgactcgggggaaagt	G/A	gaaaggagaatgcagccgat		rs1045217
i-GPR4-7	3' UTR	1	1914	ctgccggaggagtagtgcc	A/G	gaaaggttgggaaagaagg		
i-GPR4-8	3' UTR	1	1681	gaaggtagattttttt	T/del	ccaacaagfaggataaaagtc		
G protein-coupled receptor 10								
i-GPR10-1	5' Flanking region		-1701	gcttctaaaggaggagctta	T/C	aaaaggccccctctcccctgg		rs4440948
i-GPR10-2	5' Flanking region		-517	ctagttctctaaacaccagg	C/T	atggcagagcgcgctccacc		
i-GPR10-3	5' Flanking region		-462	atggagcttgagtgggggg	T/C	ggagctgagggagagcgcctc		rs1538265
i-GPR10-4	5' Flanking region		-62	ggaggggcgcgctggtgta	A/G	gaggtcggatgaggtatggc		rs3740551
i-GPR10-5	Coding region	1	615	tatcacgtgagctcaagcc	G/T	cacgcagctggcctctgaga	Pro205Pro	

^aNucleotide numbering is according to the mutation nomenclature (den Dunnen and Antonarakis 2000)

^bBoth 5' and 3' flanking sequences to each variation are denoted by *small letters*

^cVariation is shown by a *capital letter*

^dNucleotide numbering of 903-911(AGAGGAGGA/del) in exon 1 of the *ADR42B* gene was according to a cDNA sequence NM_000682.2

^eNucleotide numbering of a -550C/T SNP was according to a cDNA sequence NM_000916.2

for A/C, and 6% for A/T; transitions occurred 2.1 times more frequently than transversions. By comparing SNPs detected in this study with previous reports from elsewhere (Sturm et al. 2001; Lubrano-Bertheliet et al. 2003; Schalin-Jantti et al. 2003) or with the dbSNP database at NCBI, we were able to consider 132 of the 300 SNPs (44%) to be novel as of the end of December 2003.

We also identified two novel nonsense mutations in the Japanese healthy donors. One is a 322C → T (Arg108Stop) in *ADORA3* belonging to adenosine receptor gene family. The other is a 706C → T (Arg236Stop) in an anonymous G protein-coupled receptor 1 gene. Both SNPs, each of which was identified in a single individual among the 48 volunteers tested, would be predicted to lack nearly half of the C-terminal part of each gene product. However, since these mutations were found in the healthy donors, we have no information regarding its potential effects on the carrier's susceptibility to any diseases or drug responses. In all cases, more detailed genetic and functional studies will be necessary to clarify a relationship between these mutations and functional properties of these receptors.

Altogether, we have collected a total of 333 genetic variations, including 300 SNPs and 33 genetic variations of other types, among the 23 genes encoding G-protein coupled receptors by screening 96 Japanese chromosomes. We hope our SNP catalog can contribute to further investigations for identifying genes associated with drug efficacy and/or adverse drug reactions and for designing personalized medical care.

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