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## Identification of 156 novel SNPs in 29 genes encoding G-protein coupled receptors

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**Abstract** We have been performing extensive screening on single nucleotide polymorphisms (SNPs) in and around genes encoding drug metabolizing enzymes, transporters, and receptors and have constructed the high-density SNP maps of such gene regions. In addition to genetic information reported earlier, we identified a total of 390 genetic variations, 358 SNPs and 32 genetic variations of other types, detected in 29 genes encoding G-protein coupled receptors in Japanese populations. Following a comparison of our data with SNPs in the dbSNP database in the US National Center for Biotechnology Information, 156 SNPs from these gene loci are considered to be novel. The fine-scale SNP maps constructed in this study should serve an important resource for studies of linkage-disequilibrium mapping for complex genetic diseases and drug-response phenotypes.

**Keywords** Single nucleotide polymorphism (SNP) · G-protein coupled receptor genes · Japanese population · High-density SNP maps

### Introduction

The G-protein coupled receptors (GPCRs) represent the largest class of cell-surface receptors that recognize extracellular messengers. All members of the GPCR

family, which consists of approximately 950 members in humans (Takeda et al. 2002), are predicted to share seven predicted  $\alpha$ -helical transmembrane domains, extracellular N-termini and intracellular C-termini, and several conserved structure motifs (Howard et al. 2001). Since these receptors mediate important cellular signals, their mutations and polymorphisms are shown to be responsible for or associated with a large number of diseases. They are also known to be the targets of therapeutic agents; 50% of all modern drugs are considered to target GPCRs (see reviews by George et al. 2002; Spiegel 1995).

To establish “personalized medicine” on the basis of individual genetic variations, we have systematically explored single nucleotide polymorphisms (SNPs) in the genomic regions corresponding to drug-related genes (Iida et al. 2001a–e, 2002a–d, 2004b; Saito et al. 2001a, 2001b, 2002a–d, 2003a; Sekine et al. 2001). As a part of this program, we previously reported SNPs in genomic regions corresponding to genes encoding GPCRs and other known drug targets and constructed fine-scale SNP maps containing more than 1,100 SNPs in 63 genes (Iida et al. 2003, 2004a, 2004b; Saito et al. 2003b). We further extended our SNP discoveries of the GPCRs in 96 chromosomes from healthy Japanese donors and here report a total of 156 novel SNPs and 32 genetic variations of other types for 29 additional members of the GPCR gene family *GPR5-9*, *GPR11-18*, *GPR20*, *GPR21-27*, *GPR29-31*, *GPR34*, *GPR35*, and *GPR37*, *GPR39*, and *GPR40*.

### Subjects and methods

Samples of peripheral blood were obtained with written informed consent from 48 healthy Japanese volunteers. Polymerase chain reaction (PCR) experiments and DNA sequencing were performed according to methods described previously (Iida et al. 2003). In brief, on the basis of genomic sequences corresponding to each of GPCR from the Genbank database in the US National

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Center for Biotechnology Information (NCBI), we designed primers to amplify all selected genes in their entirety, excluding only regions that corresponded to repetitive sequences as well as intron 1 of *GPR39* because it is very long, at 227 kb. Each 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, CA, 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. All gene names and gene symbols mentioned in this report are according to the nomenclature in LocusLink of the NCBI.

## Results and discussion

Sequencing of an approximately 183.3-kb genomic region corresponding to the 29 *GPCR* loci in 96

Japanese chromosomes identified a total of 390 genetic variations, 358 SNPs and 32 genetic variations of other types (Table 1). The overall distribution of SNP was one in every 512 nucleotides on average. By comparing our data with the SNPs deposited in the dbSNP database in the NCBI (as of the end of December 2004), we judged 156 SNPs to be novel (Tables 1, 2). The exon-intron organization of each gene and locations of SNPs identified within each locus are shown schematically in Fig.1; detailed information is given in Table 2. Sub-regional distributions of novel SNPs were as follows: 44 in 5' flanking regions, five in 5' untranslated regions (UTRs), 11 in coding regions, 47 in introns, 12 in 3' UTRs, and 37 in 3' flanking regions. The overall frequencies of nucleotide substitutions were counted as 28% for A/G, 28% for C/T, 17% for A/C, 14% for C/G, 9% for G/T, and 4% for A/T. The transitions occurred 1.3 times more frequently than transversions. In addition, of the 19 SNPs in coding regions, we found a total of eight novel nonsynonymous substitutions: 404A>T (Tyr135Phe) in exon 1 of *GPR7*, 217C>G (Leu73Val) in exon 2 of *GPR11*, 149C>T (Ala50Val) in exon 1 and 371G>A (Arg124His) in exon 1 of *GPR14*, 235G>T (Ala79Ser) in exon 2 of *GPR16*, 343G>A (Val115Ile) in exon 1 of *GPR21*, 1201G>A (Gly401Arg) in exon 2 of *GPR24*, and 743G>A

**Table 1** Summary of genetic variations identified in 29 genes encoding GPCRs. SNP Single nucleotide polymorphism

Gene symbol	Accession number (genome DNA)	SNP	Genetic variations of other types	Total	Nonsynonymous substitution	Identity of SNP in dbSNP database	Novel SNP
<i>GPR5</i>	AC099782.2	4	0	4	0	3	1
<i>GPR6</i>	AL591076.5	6	0	6	0	3	3
<i>GPR7</i>	AC087348.6	6	0	6	1	3	3
<i>GPR8</i>	AL121581.41	12	1	13	1	5	7
<i>GPR9</i>	AL590763.1	3	0	3	0	0	3
<i>GPR11</i>	AC114962.2	15	0	15	2	9	6
<i>GPR12</i>	AL159978.14	6	3	9	0	2	4
<i>GPR13</i>	AC104850.2	25	1	26	2	14	11
<i>GPR14</i>	AC132938.9	5	0	5	2	1	4
<i>GPR15</i>	AC021660.16	11	1	12	1	9	2
<i>GPR16</i>	AL096870.5	9	1	10	1	5	4
<i>GPR17</i>	AC010976.5	26	0	26	0	15	11
<i>GPR18</i>	AL160155.19	8	1	9	0	5	3
<i>GPR20</i>	AC100803.10	9	3	12	1	7	2
<i>GPR21</i>	AC007066.4	2	2	4	1	0	2
<i>GPR22</i>	AC002381.1	4	2	6	0	2	2
<i>GPR23</i>	AL590083.8	4	0	4	0	2	2
<i>GPR24</i>	Z86090.10	3	0	3	1	1	2
<i>GPR25</i>	AC099756.2	14	4	18	0	9	5
<i>GPR26</i>	AC009987.17	60	2	62	0	31	29
<i>GPR27</i>	AC096970.2	2	2	4	0	1	1
<i>GPR29</i>	AL121935.17	32	1	33	0	19	13
<i>GPR30</i>	AC091729.4	22	4	26	2	15	7
<i>GPR31</i>	AL121935.17	12	0	12	0	5	7
<i>GPR34</i>	AL627402.10	4	0	4	0	3	1
<i>GPR35</i>	AC124862.4	12	0	12	2	6	6
<i>GPR37</i>	AC004925.1	25	3	28	0	16	9
<i>GPR39</i>	AC098800.3	9	1	10	1	6	3
<i>GPR40</i>	U62631.2	8	0	8	1	5	3
Total		358	32	390	19	202	156

**Table 2** Identification of 156 novel single nucleotide polymorphisms and 32 genetic variations of other types in 29 GPCR loci found among 96 Japanese chromosomes

Gene symbol	Location	Exon	Position <sup>a</sup>	5' Flanking sequence <sup>b</sup>	Variation <sup>c</sup>	3' Flanking sequence <sup>b</sup>	Substitution
G protein-coupled receptor 5							
i-GPR5-1	5' Flanking region		-1759	aaatagtagtgtgtctg	A/T	tcctgtcaaatgccctg	
G protein-coupled receptor 6							
i-GPR6-1	5' Flanking region		-840	gtcaatctgcagcgcgcgc	G/A	ctcgcagccgcttttctgc	
i-GPR6-2	5' Flanking region		-708	tgctctgt(C/T)tgccggggag	C/A	tcagcccggcggccgcctc	
i-GPR6-3	3' Flanking region		35	gtcctctcaccaacaccaca	C/T	cccaacaagccagcctttgg	
G protein-coupled receptor 7							
i-GPR7-1	Coding region	1	404	cgtcatgagcggcggcgcgt	A/T	cctgggtgtgtggcactg	Tyr135Phe
i-GPR7-2	3' Flanking region		535	cgcgcgctttggcggccac	C/T	cctgtgagaccgcttggcc	
i-GPR7-3	3' Flanking region		1758	aaaaaactcccccttggaa	G/A	gggggaagcaaacacctct	
G protein-coupled receptor 8							
i-GPR8-1	5' Flanking region		-127	gctgtgcctaacagacggc	C/T	ggatctcaaatgtctgtgt	
i-GPR8-2	3' Flanking region		19	gaaggcctggccaccatca	C/T	ccccatcatatgccatca	
i-GPR8-3	3' Flanking region		445	acctacagacagccgtggc	A/G	tatacctcccat(G/A)tctctgc	
i-GPR8-4	3' Flanking region		458	cgtgggc(A/G)tatacctccat	G/A	tctctgcttc(T/C)ggacagcc	
i-GPR8-5	3' Flanking region		470	cctcccat(G/A)tctctgcttc	T/C	ggacagccctgggtggaca	
i-GPR8-6	3' Flanking region		697	ctcccaagatggggccggg	G/A	ggtgtaagtggggcact	
i-GPR8-7	3' Flanking region		833	ccagcaggagggccagcccc	G/A	ccgtgccatgtgcatggc	
i-GPR8-8	3' Flanking region		752~753	ctgtgtgctgcaaaagcgg	GG/ins	acacctgaccgcatgagac	
G protein-coupled receptor 9							
i-GPR9-1	Intron 1		213	ctcctctctctctggcttc	G/A	gtgtctctgtgcaaaatgg	
i-GPR9-2	Intron 1		234	gtgtctctgctcaaaatgg	G/A	ggggcggggggcaagtaga	
i-GPR9-3	Intron 1		707	ggcagagagggctctgggca	C/G	tggaggagcgtcttcttcc	
G protein-coupled receptor 11							
i-GPR11-1	5' Flanking region		-155	aaccccgcccgcagggcgt	C/G	ccgcagtctaaggacctgg	
i-GPR11-2	5' Untranslated region	1	-53	tccagtggagctctgagttt	C/G	gaatcgg(C/T)ggcggcgattc	
i-GPR11-3	Intron 1		317	tgggttcgggaaaggagg	G/A	aaggaaggagtagctgtgc	
i-GPR11-4	Intron 1		735	tacgagcggaaacttttgg	C/T	cctgcttatatttgaccag	
i-GPR11-5	Intron 1		1164	ggaattagatggaagaatgt	G/C	attctttccctctgcagtt	
i-GPR11-6	Coding region	2	217	catctgtcctcactggaaaa	C/G	tgacctatgtcttctcca	Leu73Val
G protein-coupled receptor 12							
i-GPR12-1	5' Flanking region		-1571	gtttctcatcttagaatcca	T/C	tgatgtggcaaaatgaaaa	
i-GPR12-2	5' Flanking region		-702	ccggagcccggccgcccc	G/C	ctgccacagcgggcaactg	
i-GPR12-3	5' Flanking region		-379	agccc(TC/del) ttgttccggtcg	G/A	gggtgctgttgaggatgtgc	
i-GPR12-4	3' Flanking region		705	tactttcaaaatgaatcct	G/A	aagtaggttttagattctat	
i-GPR12-5	5' Flanking region		(-914)~ (-913)	ctgaccctgtggggcgcgcg	CG/ins	gcctgcggggatccccggg	
i-GPR12-6	5' Flanking region		(-849)~ (-822)	ggggcgggggcgcgcgcg	GCGGGG AGCGTGT GGGCCGG GCGGGCG	ggcggggaaagctggcgcg	
i-GPR12-7	5' Flanking region		(-394)~ (-393)	cggggggagcttgagcccc	C/del TC/del	ttgttccggtcg(G/A)gggtgc	
G protein-coupled receptor 13							
i-GPR13-1	5' Flanking region		-990	taaggagcaccggatgtgg	C/T	tgggatgtggcagcaagg	
i-GPR13-2	5' Flanking region		-232	agggcctgctccctgcccc	C/A	acctcaggttgggtaagt	
i-GPR13-3	5' Flanking region		-188	acctctctccctcagctcc	G/A	cagtctcctgaggtttag	
i-GPR13-4	Intron 1		7921	ggtttctagtgtccctcagg	G/A	(A/G)caaaagaaagccatggtcc	
i-GPR13-5	Intron 1		7922	gittctagtgtccctcagg(G/A)	A/G	caaaggaaagccatggtcca	
i-GPR13-6	Intron 1		10113	ccagatggctcatagcagg	A/G	ccatgatatgctgggtgagc	
i-GPR13-7	Intron 1		11819	tggaaagcagaaagtacac	A/G	ccctgctgggtggccctc	
i-GPR13-8	Intron 1		12230	gtaggggaaatagtcacc	A/G	gagactagcccagcagacta	
i-GPR13-9	Coding region	2	456	ggcgtcaccatcagcctagg	C/T	gtctggcagcagcatttt	Gly152Gly
i-GPR13-10	3' Untranslated region	2	1396	attgtggcacaagcaaaagg	G/A	tgtctgagccctcaaaagtga	
i-GPR13-11	3' Flanking region		1869	gatggagcatataggctttc	G/A	gttactaagaagagctatca	
i-GPR13-12	3' Flanking region		1686~1689	ggtgggtcaagacttagaca	GACA/del	ggccactgtggagggacagc	
G protein-coupled receptor 14							
i-GPR14-1	5' Flanking region		-266	cctgctgggcatgccccgg	T/A	cggggaggggggttgggca	
i-GPR14-2	Coding region	1	149	ctccctggaggacctgtgg	C/T	cacgggcaccattgggactc	Ala50Val
i-GPR14-3	Coding region	1	371	cttcggggagctggcctgcc	G/A	cgtgctcttccgctggact	Arg124His
i-GPR14-4	3' Flanking region		393	ttgccactggaacaatcaac	C/G	ctgagctggcttccgtgctc	
G protein-coupled receptor 15							
i-GPR15-1	5' Flanking region		-646	aaatgctatgcaagtgtga	A/G	tggaaaacttaaaataataa	
i-GPR15-2	3' Flanking region		862	cataaatgcttagctgtac	C/G	ccgatgacgattatcat	

Table 2 (Continued)

Gene symbol	Location	Exon	Position <sup>a</sup>	5' Flanking sequence <sup>b</sup>	Variation <sup>c</sup>	3' Flanking sequence <sup>b</sup>	Substitution
i-GPR15-3	3' Flanking region		670	ttataagatatattgataaaa	A/del	tgtatctcattcataatggt	
G protein-coupled receptor 16							
i-GPR16-1	5' Flanking region		-1379	attatgaggggtgatggt	C/T	cctgtaaggactattgtgt	
i-GPR16-2	5' Flanking region		-901	agtatgagacaggcacacaa	G/A	gagtggaccagtgttaggg	
i-GPR16-3	5' Untranslated region	2	-4	actctccaggtcctcccgac	G/T	gccatgaacctacatcttc	
i-GPR16-4	Coding region	2	235	ccttttctcacttctctg	G/T	cccaaggcacctggagtttt	Ala79Ser
i-GPR16-5	5' Flanking region		-1155	ccagccttcagtggcatctt	G/del	acctgccctcctcagcccag	
G protein-coupled receptor 17							
i-GPR17-1	5' Flanking region		-1856	acaagagaggaaggagcct	C/T	gggggcatcatctcccctc	
i-GPR17-2	5' Flanking region		-1835	ggtgggcatcatctcccctc	G/A	actactggccagagccctgg	
i-GPR17-3	5' Flanking region		-1768	gttgtggcctgtggcttcag	T/C	cttcatcaccacaatccctg	
i-GPR17-4	5' Flanking region		-1417	aataacagaaaggctgtgag	C/T	ccagaaatgccctgctcagg	
i-GPR17-5	5' Flanking region		-1294	gacctgcgccccggctcaga	C/T	acctcacaccagctggctc	
i-GPR17-6	Intron 1		62	taagcagaggaaacctcag	C/T	ggggagccctgccaggggag	
i-GPR17-7	3' Untranslated region	3	1112	gtcagagctgtgagcggggg	G/C	(C/A)gccgtccaggc (C/T)gagcgca	
i-GPR17-8	3' Untranslated region	3	1113	tcagagctgtgagcggggg (G/C)	C/A	gccgtccaggc(C/T)gagcgca	
i-GPR17-9	3' Untranslated region	3	1125	gcggggg(G/C)(C/A) gccgtccaggc	C/T	gagcgagactgttaggac	
i-GPR17-10	3' Untranslated region	3	1945	cctaacaatgtcctttttgt	A/G	tttgtttgacggaccataa	
i-GPR17-11	3' Flanking region		381	ccctgtcggcgactgtgctg	G/A	tcagcacgagctcctggtgc	
G protein-coupled receptor 18							
i-GPR18-1	5' Flanking region		-1356	gcaaaggacagattaggctt	G/T	catgcaggcagatttctgtc	
i-GPR18-2	5' Flanking region		-1124	aatttctcatccacacaag	A/G	aatagttgctatggtgtct	
i-GPR18-3	5' Untranslated region	1	-306	aagagctattttaacagaag	C/A	aactcaaagatatcccttcg	
i-GPR18-4	Intron 2		279	atgagaattactgtgaatgt	T/del	cagtagttaaccagttgaat	
G protein-coupled receptor 20							
i-GPR20-1	3' Flanking region		113	ctcgattgattggtgatggc	T/C	accagagcac(C/T)gcattgag	
i-GPR20-2	3' Flanking region		125	gtgatggc(T/C)accagagcac	C/T	gcattgagcgtctaaggcca	
i-GPR20-3	5' Flanking region		(-1189)~ (-1188)	cacgagcctccccacctgc	C/ins	tggcccaaaagacttctct	
i-GPR20-4	3' Flanking region		1019	aacagccattttctcccc	C/del	gggggcagagaggacgtgac	
i-GPR20-5	3' Flanking region		1480	cagtttagggctcctggactt	T/del	atatccccatgttacaatg	
G protein-coupled receptor 21							
i-GPR21-1	Coding region	1	343	tagtatcagttctgaagagc	G/A	tctcatggcttctctggcc	Val115Ile
i-GPR21-2	3' Flanking region		280	ggaaatgactacagttctca	G/C	atttaaaatgaataaagcca	
i-GPR21-3	3' Flanking region		24~67	ggctcagttacggggttccc	(GT)16~22	atttatctctaagtattcc	
i-GPR21-4	3' Flanking region		1212	ttaatggctttttttttt	T/del	cctgcaaaagtactagaaaa	
G protein-coupled receptor 22							
i-GPR22-1	5' Flanking region		-698	tttagcataatgtcccaactt	G/C	tttaatttttaagtttggc	
i-GPR22-2	3' Flanking region		217	gttaaagtactatcatgtgt	A/G	tattttgtcaatattatgtc	
i-GPR22-3	3' Flanking region		822	ttaatatagtgcaatgattt	T/del	aaaaaaaaaaaaaaaaaaaa	
i-GPR22-4	3' Flanking region		952	taccaggaatgaaaaaaaaa	A/del	gactttaaatcattatagaa	
G protein-coupled receptor 23							
i-GPR23-1	3' Untranslated region	1	1227	atgcaccaaatccagtcaga	T/C	acattttgttgaaggtatac	
i-GPR23-2	3' Flanking region		985	atctgtgtctgggttaggaa	C/T	aaagtgaaaaaatgctaaaa	
G protein-coupled receptor 24							
i-GPR24-1	Intron 1		240	aggggggcccagcgtgagac	A/C	gcaggggaaggtcgtctgt	
i-GPR24-2	Coding region	2	1201	cggtgaagcctcagcccag	G/A	ggcagcttcgcgtgtcagc	Gly401Arg
G protein-coupled receptor 25							
i-GPR25-1	5' Flanking region		-594	accagatctgctgtgtccc	G/A	gcagtggagtcttcttagg	
i-GPR25-2	5' Flanking region		-160	gcctgccctcccaccceat	C/G	ccctcctcctcccctttt	
i-GPR25-3	3' Flanking region		886	actctcgaggtgagtaatc	C/T	cacaggaggaagcaatcat	
i-GPR25-4	3' Flanking region		1054	accagggcccc(C/ins)ttttt	T/A	t(T/del)ctatctttttcagacct	
i-GPR25-5	3' Flanking region		1800	aacagacaggaagaagaag	A/G	cttctcatgccctggtggg	
i-GPR25-6	5' Flanking region		(-1170)~ (-1169)	acctggggcagactcaga	GA/ins	gggactgtgacatcagttc	
i-GPR25-7	3' Flanking region		60~61	agaggaggccaga (G/T)gtccc	CCCG/ins	gggggactgagctcccag	
i-GPR25-8	3' Flanking region		1047~ 1048	aatatataaccagggcccc	C/ins	ttttt(T/A)t(T/del)ctatcttttt	
i-GPR25-9	3' Flanking region		1056	caggcccccc(C/ins)ttttt (T/A)t	T/del	ctatctttttcagaccttc	

Table 2 (Continued)

Gene symbol	Location	Exon	Position <sup>a</sup>	5' Flanking sequence <sup>b</sup>	Variation <sup>c</sup>	3' Flanking sequence <sup>b</sup>	Substitution
G protein-coupled receptor 26							
i-GPR26-1	5' Flanking region		-808	ctgccaggatagcatgcagg	C/A	ggggacaggtggcactgggg	
i-GPR26-2	5' Flanking region		-178	gccagggttcactgccgcgc	G/T	ccaggtgctgccccgtgagg	
i-GPR26-3	5' Flanking region		-15	cgccggccgaggggctga	G/A	ccggccggggcagcgcgat	
i-GPR26-4	Intron 1		190	gcaaacaggggccacaaaa	A/C	tgggggtgagccatctata	
i-GPR26-5	Intron 1		704	ctgaatctgccccacctcc	G/A	tcgtcacgc(T/A)ggctgctgtt	
i-GPR26-6	Intron 1		714	ccccactcc(G/A)tcgtcacgc	T/A	ggctgctgttctcaggagg	
i-GPR26-7	Intron 1		2352	ctacaaaigagcaagtacag	A/G	gctagctcaggggctgcccc	
i-GPR26-8	Intron 1		2958	ggccccagggtatggttga	G/A	ggaccttgcctctccctgac	
i-GPR26-9	Intron 1		6328	gcattttttaacagactgc	C/T	tatttttgagccaggccac	
i-GPR26-10	Intron 2		90	ggcagcctctcttgccaca	C/G	gttctctgcacggtgtgt	
i-GPR26-11	Intron 2		3945	cacagtcaccctccaggagc	C/T	tgatgcaaacattccat	
i-GPR26-12	Intron 2		4089	acttatcatccactctggaa	T/C	ccggatcactgacattcca	
i-GPR26-13	Intron 2		6453	aaacggatgctgcagtttc	C/T	gagatgactgaaaccaagt	
i-GPR26-14	Intron 2		6486	accaagttgttcattgttca	C/G	ttacaccttcattgagctg	
i-GPR26-15	Intron 2		6624	tgtcaagagttaggttgac	G/A	tcagatggcagctgggaatg	
i-GPR26-16	Intron 2		8677	cttaggctgctgggtggaa	T/G	gtgaggtccccatgggtgag	
i-GPR26-17	Intron 2		9098	tctccccagctccatccct	C/A	ccccaacctgatctgctgac	
i-GPR26-18	Intron 2		9155	acccaaggggatttccggg	G/T	g(G/C)agctgtgtcaggcaggc	
i-GPR26-19	Intron 2		9157	cccaggggatttccggg(G/T)g	G/C	agctgtgtcaggcaggcat	
i-GPR26-20	Intron 2		10103	ctgctgctcccacgtccc	G/A	tcttgagaccatccactaac	
i-GPR26-21	Intron 2		10371	gctcatccagatgcctgccc	G/A	gatctggaattgaaagaag	
i-GPR26-22	Intron 2		10434	cttgctcttctcatcaacg	A/G	aaaggactggggctgtcag	
i-GPR26-23	3' Untranslated region	3	3953	cagaatttgccttttaagt	C/T	acgtgcaactattccggct	
i-GPR26-24	3' Untranslated region	3	4841	atctaggtttcaattgtctt	G/A	tatcttccctaattctcca	
i-GPR26-25	3' Untranslated region	3	4951	ccatgaaattgcaaaaacc	A/G	tcttcattcctttttatggg	
i-GPR26-26	3' Untranslated region	3	6265	gacctcttgcacctgcag	C/T	cgggagaactgacttagagg	
i-GPR26-27	3' Flanking region		1154	attattaatagtaaccaaac	T/C	ctctgcttaacaaccttcg	
i-GPR26-28	3' Flanking region		1629	aacacactcatttcgccaca	C/T	ggaggcttactctgccac	
i-GPR26-29	3' Flanking region		1658	tactctgccagtgccaa(T/C)	G/A	ggagaaccatcccttccctt	
i-GPR26-30	Intron 2		9181~9182	gtgtcagggcagggcatgga	A/ins	gccttttgagcacataagca	
i-GPR26-31	3' Untranslated region	3	4123	accaatcacctgctgtttt	T/del	acttagaagcaggcttggg	
G protein-coupled receptor 27							
i-GPR27-1	5' Flanking region		-424	cgccggccgcgctgcgcgct	C/G	cgccggaggggagggggctc	
i-GPR27-2	5' Flanking region		(-173)~(-172)	cctgagatggcggcggcggc	GGC/ins	acagcggcggctcggggagc	
i-GPR27-3	3' Flanking region		1151~1154	gaactataatttaataata	TTTC/del	ttttagacattataatgt	
G protein-coupled receptor 29							
i-GPR29-1	5' Flanking region		-1614	acctccagatccctgctct	G/T	tgcagtctaacaagggggc	
i-GPR29-2	5' Flanking region		-1486	aacgcgggtttgttcaacac	G/A	ttacatttctgctaataaa	
i-GPR29-3	Intron 2		2531	tttcatcttaaatgaatta	G/A	ccaattaattattacttct	
i-GPR29-4	Intron 2		2578	ctctattgcatattgtacct	A/G	ataaaaagttgactaggaag	
i-GPR29-5	Intron 2		6953	catagggaccacgtgtgaga	T/C	aggaaagtctgtaacctcaaa	
i-GPR29-6	Intron 2		7615	tagtgtcttatgaacaggac	G/A	gagtagggcagcttctcata	
i-GPR29-7	Intron 2		12132	gatgcctctgccacagcaga	T/G	tcatgcttgcacctggaat	
i-GPR29-8	3' Untranslated region	4	2680	gcactccagcctgggtgaca	A/G	agcgagactccatctcaaaa	
i-GPR29-9	3' Untranslated region	4	3450	attgattctcccatactt	T/G	ttgctctcaggctctggccg	
i-GPR29-10	3' Flanking region		123	atgtgttagaacctccaagt	A/G	ttcaattatttctggatagc	
i-GPR29-11	3' Flanking region		1208	aggccagccctattctgcc	C/T	cctatttataaacagagc	
i-GPR29-12	3' Flanking region		1251	teaaggctcatgacttcagc	G/A	gggctctgtgttcttaaat	
i-GPR29-13	3' Flanking region		1848	gagtcagggtggacagtcag	A/G	aatgatgggcagagtgtgt	
i-GPR29-14	Intron 2		11431~11432	gatatgacacagtggtgggg	G/ins	cgaggaggcagttccactt	
G protein-coupled receptor 30							
i-GPR30-1	5' Untranslated region	1	-436	atgaggcagttcagcggccc	C/T	gagagtccggggaggagggt	
i-GPR30-2	Intron 1		825	agaggagccagagaggagc (CAGAGAGGAGC/ins)	G/T	ggggcggagggggcctataaa	
i-GPR30-3	Intron 1		1253	gcacagaccctctcccccg	G/C	agctccggtggtctcagcgt	
i-GPR30-4	Coding region	2	30	acttccaagaagccggggcgt	G/A	ggcctggagatgtacc (C/T)agg	Val10Val
i-GPR30-5	Coding region	2	743	ggtcagggcgaccggcacc	G/A	tgggctcggccccggcggc	Arg248His

Table 2 (Continued)

Gene symbol	Location	Exon	Position <sup>a</sup>	5' Flanking sequence <sup>b</sup>	Variation <sup>c</sup>	3' Flanking sequence <sup>b</sup>	Substitution
i-GPR30-6	3' Flanking region		1391	ctccttccaggccccaggga	C/T	gagacttgcctctccc	
i-GPR30-7	3' Flanking region		1707	cattccccacacacagtccc	G/A	ttcacatagcttcaacaggg	
i-GPR30-8	Intron 1		824~825	gagaggagccagagaggagc	CAGAGA GGAGC/ins	(G/T)gggcgagggggg cctataa	
i-GPR30-9	Intron 1		3739~3740	ggaccactctctctctc	TC/ins	agaaacactggttccctt	
i-GPR30-10	3' Untranslated region	2	1462~1463	tgccgctgcaggaaacattt	CT/del	gacaccctgcaccaggaag	
i-GPR30-11	3' Flanking region		205~206	atgccgtggggcacttctg	TG/del	tcatgcttgggtgccatgac	
G protein-coupled receptor 31							
i-GPR31-1	5' Flanking region		-1029	caagatgaagtgggtcaac	G/T	ttgagtgaagaccaggatga	
i-GPR31-2	5' Flanking region		-876	agggtaatgatgactgcaca	C/T	gtttattcatcaagaaatg	
i-GPR31-3	5' Flanking region		-753	taactttctagtggattcta	C/T	gcatttttacaagccattga	
i-GPR31-4	5' Flanking region		-178	ccctgctcatcctcttccc	C/G	aatgaattttggttctg	
i-GPR31-5	3' Flanking region		840	gaaatggtcattccaaccc	C/T	(G/A)ctggcacagctggtggaca	
i-GPR31-6	3' Flanking region		1320	ccaagctttctgcaaatc	G/A	aggccaataatgatgctct	
i-GPR31-7	3' Flanking region		1939	tgccctgtaggaatagacc	C/G	cacaggtgggacagatgcc	
G protein-coupled receptor 34							
i-GPR34-1	5' Flanking region		-774	gtgtaccagaataatag	A/G	atgttagatacagcccaatg	
G protein-coupled receptor 35							
i-GPR35-1	5' Flanking region		-1623	aaaagtccctggaacgaggg	T/A	gaagtgtgctcatgatca	
i-GPR35-2	5' Flanking region		-1044	tgtgagtctggactctggg	C/T	gctcaccagcagctccgtct	
i-GPR35-3	5' Flanking region		-788	tgggtggtcctgatagtgac	G/A	gagaggaggatactcagctc	
i-GPR35-4	5' Flanking region		-765	gaggaggatactcagctcca	C/T	ccctggcgcccccctgagca	
i-GPR35-5	5' Flanking region		-258	ccttctgctcctttctctgc	C/G	ccatgacagcaggcagatcc	
i-GPR35-6	3' Flanking region		1485	ccctgcccaggaggtccat	G/T	cccaggaggctccatgtcaa	
G protein-coupled receptor 37							
i-GPR37-1	5' Untranslated region	1	-271	aaggtcagcccaccgggagta	G/A	cctattccctctaggaacct	
i-GPR37-2	Intron 1		7888	gattgaatcaagaaagaaat	T/G	tccttaacagactaccaata	
i-GPR37-3	Intron 1		8124	ggtaaggaactgaaattcca	G/C	gtcactttaagattgactag	
i-GPR37-4	Intron 1		8698	atattagaataaataatggta	T/C	ttattatattgtggccatc	
i-GPR37-5	Intron 1		9356	ggtagaaaatttctctattt	T/C	ataaaaaccagtgatttcta	
i-GPR37-6	Intron 1		9917	cctagggaacatgggactt	G/A	aaattactgaaaatctgga	
i-GPR37-7	Intron 1		10564	ttgaatattgaacatctgga	A/G	tgtcacttgaataatctgga	
i-GPR37-8	3' Flanking region		1096	tcaacaaggtgcccttctc	T/G	tctttagatccctgtaata	
i-GPR37-9	3' Flanking region		1450	tggaaataggggaatgctta	T/C	agggttagaagagagcatga	
i-GPR37-10	Intron 1		5849~5851	tttctctt(G/T)ccattgatcat	AAT/del	gagaatgtgctcttcttaa	
i-GPR37-11	Intron 1		8929~8932	gatctgcatacactccaata	TTAA/del	gacctttgcaaaaggctcat	
i-GPR37-12	Intron 1		9433~9434	ataggaaggaaatttctt	AGA/ins	aggacactgttctgttttt	
G protein-coupled receptor 39							
i-GPR39-1	Coding region	1	537	gccatgggtactgagtacc	C/T	ctggtgaacgtgcccgcca	Pro179Pro
i-GPR39-2	Intron 1		53	gcttcccaaccttccccac	G/A	accctgcccactgctctgg	
i-GPR39-3	Intron 1		226495	ctgaactagaaggagtttt	A/G	tattgccaactctgaaata	
i-GPR39-4	Intron 1		226792~ 226793	catcctttaaatacaaaaca	AACA/ins	ctgcttattctaatgcagct	
G protein-coupled receptor 40							
i-GPR40-1	5' Flanking region		-1469	cagtgtcccagccatgcac	C/A	ctggggggatgctgcttgg	
i-GPR40-2	5' Flanking region		-1171	actgccacttgagatggct	T/C	catggctgcagtcacagggc	
i-GPR40-3	5' Flanking region		-873	gcgtggcctcacctcagcc	G/A	ggatccccattagctctc	

<sup>a</sup>Nucleotide numbering is according to the mutation nomenclature (den Dunnen and Antonarakis 2000)

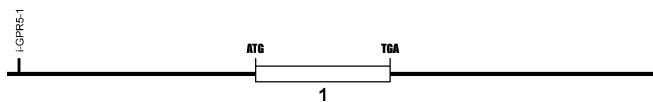
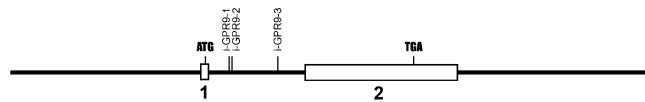
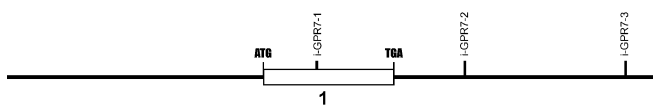
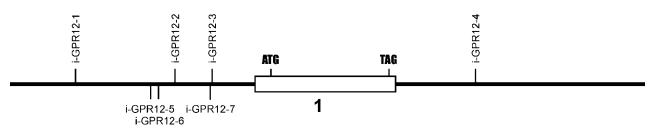
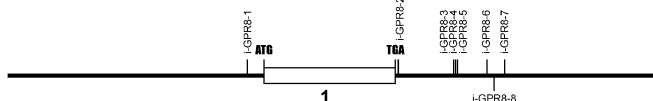
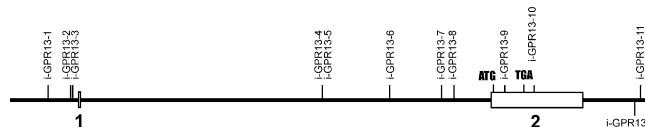
<sup>b</sup>Both 5' and 3' flanking sequences to each variation are denoted by *small letters*

<sup>c</sup>Variant nucleotide are indicated by *capital letters*

(Arg248His) in exon 2 of *GPR30*. These SNPs might effect on the function of the corresponding GPCRs.

Altogether, we have collected a total of 156 novel SNPs and 32 genetic variations of other types by screening of 29

genes encoding *GPCRs*. 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.

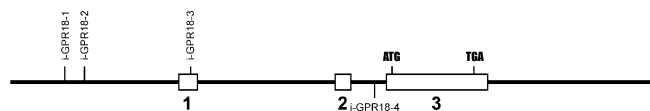
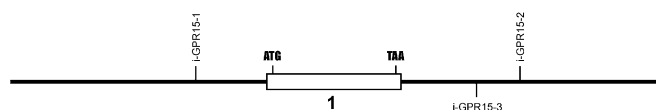
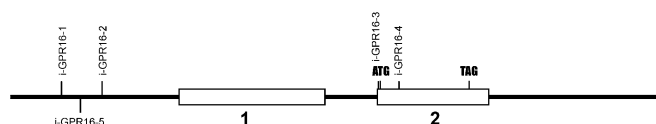
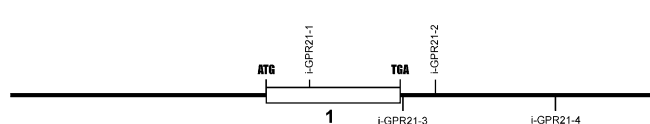
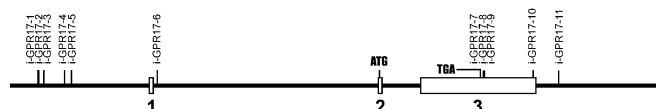
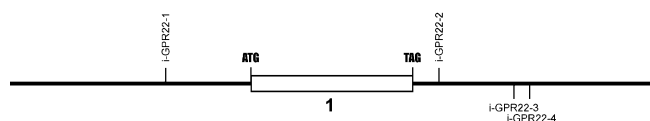
**G protein-coupled receptor 5 (GPR5): genome size 4.9-kb****G protein-coupled receptor 9 (GPR9): genome size 6.6-kb****G protein-coupled receptor 6 (GPR6): genome size 5.1-kb****G protein-coupled receptor 11 (GPR11): genome size 18.9-kb****G protein-coupled receptor 7 (GPR7): genome size 5-kb****G protein-coupled receptor 12 (GPR12): genome size 5.7-kb****G protein-coupled receptor 8 (GPR8): genome size 5-kb****G protein-coupled receptor 13 (GPR13): genome size 21.3-kb**

**Fig. 1** Fine-scale single nucleotide polymorphism (SNP) maps of 29 gene loci encoding G-protein coupled receptors (GPCRs). Exons and introns are represented by *rectangles* and *horizontal lines*, respectively. The SNPs are indicated *above the lines* (designations correspond to the left-most column of Table 2). Genetic variations

of other types, where present, are indicated *below the maps*. However, the complete 5' untranslated sequences and/or 3' untranslated sequences of *GPR5*, *GPR6*, *GPR7*, *GPR8*, *GPR14*, *GPR20*, *GPR21*, *GPR22*, *GPR25*, *GPR27*, *GPR31*, *GPR35*, *GPR39* and *GPR40* were yet unidentified in database we used

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**G protein-coupled receptor 14 (GPR14): genome size 6.3-kb****G protein-coupled receptor 18 (GPR18): genome size 7.8-kb****G protein-coupled receptor 15 (GPR15): genome size 6-kb****G protein-coupled receptor 20 (GPR20): genome size 5.2-kb****G protein-coupled receptor 16 (GPR16): genome size 7.7-kb****G protein-coupled receptor 21 (GPR21): genome size 5.1-kb****G protein-coupled receptor 17 (GPR17): genome size 11-kb****G protein-coupled receptor 22 (GPR22): genome size 5.3-kb****Fig. 1 (Continued)**

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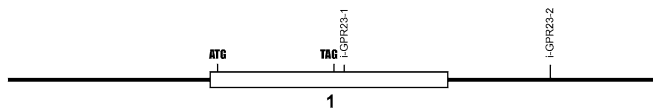
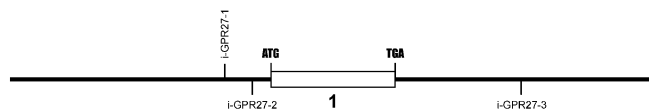
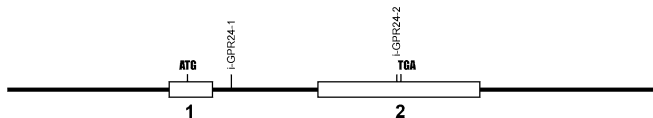
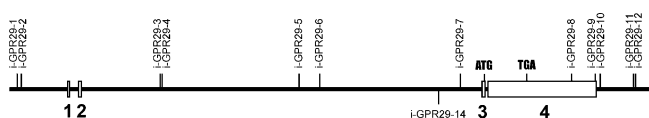
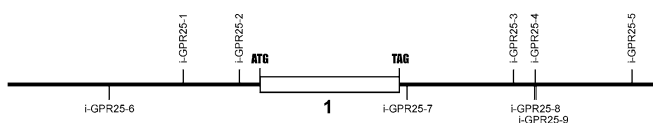
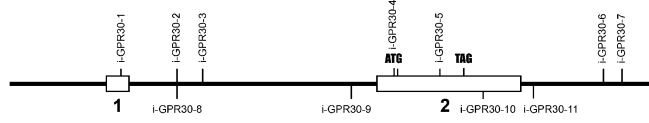
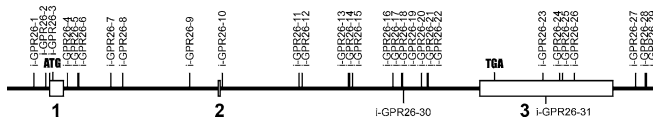
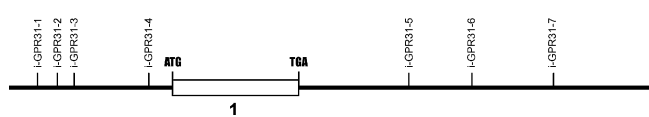
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**G protein-coupled receptor 23 (*GPR23*): genome size 6.3-kb****G protein-coupled receptor 27 (*GPR27*): genome size 6-kb****G protein-coupled receptor 24 (*GPR24*): genome size 7.6-kb****G protein-coupled receptor 29 (*GPR29*): genome size 21-kb****G protein-coupled receptor 25 (*GPR25*): genome size 5.1-kb****G protein-coupled receptor 30 (*GPR30*): genome size 11-kb****G protein-coupled receptor 26 (*GPR26*): genome size 33-kb****G protein-coupled receptor 31 (*GPR31*): genome size 5-kb****Fig. 1 (Continued)**

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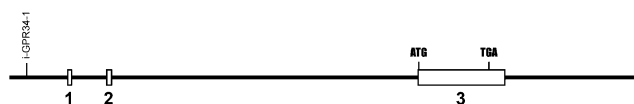
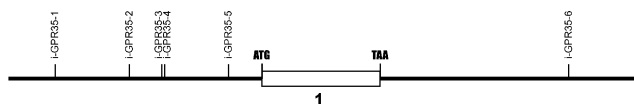
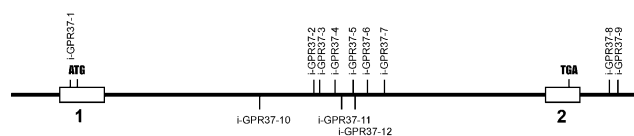
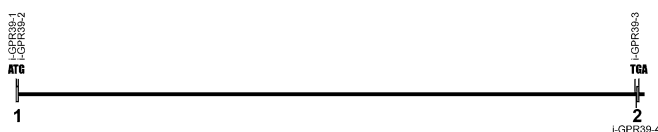
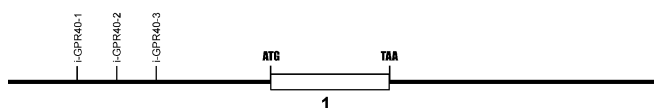
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**G protein-coupled receptor 34 (*GPR34*): genome size 12-kb****G protein-coupled receptor 35 (*GPR35*): genome size 5-kb****G protein-coupled receptor 37 (*GPR37*): genome size 24-kb****G protein-coupled receptor 39 (*GPR39*): genome size 232.6-kb****G protein-coupled receptor 40 (*GPR40*): genome size 5-kb****Fig. 1 (Continued)**

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