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Identification of single-nucleotide polymorphisms (SNPs) of human N-acetyltransferase genes *NAT1*, *NAT2*, *AANAT*, *ARD1*, and *L1CAM* in the Japanese population

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Abstract By direct sequencing of regions of the human genome containing five genes belonging to the acetyltransferase family, arylamine N-acetyltransferase (*NAT1*), arylamine N-acetyltransferase (*NAT2*), arylalkylamine N-acetyltransferase (*AANAT*), L1 cell adhesion molecule (*L1CAM*), and the human homolog of *Saccharomyces cerevisiae* N-acetyltransferase *ARD1*, we identified 53 single-nucleotide polymorphisms (SNPs) and two insertion/deletion polymorphisms in 48 healthy Japanese volunteers. *NAT1* and *NAT2* are so-called drug-metabolizing enzymes. In the *NAT1* gene we found two SNPs and a 3-bp insertion/deletion polymorphism that corresponded to the NAT1*3, *10, and *18A/*18B alleles reported in other populations. The frequencies of NAT1* alleles in our Japanese subjects were 52.6% for NAT1*4, 1.0% for NAT1*3, 40.6% for NAT1*10, 2.6% for NAT1*18A and 3.1% for NAT1*18B. In the *NAT2* gene we found 32 SNPs and a 1-bp insertion/deletion polymorphism; 6 SNPs within the coding region were reported previously and belonged to the slow acetylator group (NAT2*5, NAT2*6 and NAT2*7), and 2 of the 8 SNPs in the 5′ flanking region were reported in the dbSNP of GenBank, but the remaining 24 SNPs and the insertion/deletion polymorphism were novel. The frequencies of NAT2* alleles in Japanese (51.3% for NAT2*4, 1.6% for *5B, 26.1% for *6A, 2.2% for *6B, 1.2% for *7A, 10.1% for *7B, 7.4% for *12A, and 1.1% for *13) were significantly different from those reported in Caucasian populations. In the *AANAT* gene we found 4 novel SNPs: 2 in the 5′ flanking region, 1 in exon 4, and 1 in intron 3. In the two genes belonging to the N-terminal N-acetyltransferase family, we identified 9 SNPs, 7 of them novel, for *ARD1*, and six novel SNPs for *L1CAM*. Variations at these loci may contribute to an understanding of the way in which different genotypes may affect the activities of human N-acetyltransferases, especially as regards the therapeutic efficacy of certain drugs and antibiotics.

Key words Single-nucleotide polymorphism (SNP) · Human arylamine N-acetyltransferase (NAT1) · Human arylamine N-acetyltransferase (NAT2) · Human arylalkylamine N-acetyltransferase (AANAT) · Human L1 cell adhesion molecule (L1CAM) · Human N-acetyltransferase homolog of *S. cerevisiae ARD1*

Introduction

N-acetyltransferase (NAT), first identified as an inactivator of the anti-tubercular drug isoniazid (Hughes et al. 1954), refers to two structurally related isoenzymes called NAT1 and NAT2 (Blum et al. 1990). NAT1 specifically catalyzes acetylation for arylamine acceptor structures, such as *p*-aminosalicylic acid and *p*-aminobenzoic acid (Minchin 1995; Sim and Ward 1995). NAT2 acetylates other arylamine-acceptor structures, such as isoniazid, caffeine, procainamide, and sulfasalazine (Grant et al. 1983; Hughes et al. 1954; Reidenberg 1984; Sabbagh et al. 1997). Specific types of NAT1 and NAT2 alleles have been correlated with distinct metabolic activities, and also with the presence or absence of side effects for these drugs (Hughes et al. 1998; Lin et al. 1998; Grant et al. 1997, 2000; Hein et al. 1994, 2000; Leff et al. 1999).

Another enzyme, arylalkylamine N-acetyltransferase (AANAT), converts serotonin, as well as synthetic arylethylamine derivatives, to N-acetyl forms by transferring an acetyl group from acetyl coenzyme A. AA-NAT may play a major role in the regulation of melatonin-associated circadian rhythm in vertebrates (Delagrange and Guardiola-Lemaitre, 1997).

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The L1 cell adhesion molecule (L1CAM) shows 40% identity of amino-acid sequence with the N-acetyltransferase that is a human homolog of *Saccharomyces cerevisiae* ARD1 (Tribioli et al. 1994). N-terminal acetyltransferases, such as ARD1 and L1CAM, transfer acetyl groups from acetyl-CoA to the termini of α-amino groups during the proteolytic processing of completely translated protein and peptide hormones (Polevoda et al. 1999).

Genetic variations can alter the expression levels and/or biological function(s) of a gene product. Hence, genetic variations in genes encoding drug-metabolizing enzymes may be associated with differences in therapeutic efficacy and side effects among individual patients. We have been focusing on identifying polymorphisms in genomic regions that encode drug-metabolizing enzymes; such sites should be useful markers for studying the correlation of genotype with phenotype, as regards the activity of N-acetyltransferases. We report here the discovery of numerous novel polymorphisms in genomic DNAs encoding NAT1, NAT2, AANAT, ARD1, and L1CAM.

Materials and methods

Amplification of samples

Total genomic DNAs were isolated by phenol/chloroform extraction from peripheral leukocytes of 48 healthy Japanese volunteers who provided their informed consent. We screened all 96 chromosomes for SNPs after designing polymerase-chain-reaction (PCR) primers to amplify known N-acetyltranferase genes, including about 1 kb upstream of the predicted first exon in genes where the complete genomic DNA sequence was unknown. We eliminated genomic regions containing repetitive DNA sequences using the Repeat Masker computer program (Seki et al. 2000). Each amplification reaction was performed with 60 ng of mixed genomic DNA derived from three individuals. Total reaction volumes of 20 μl contained dNTPs (25 mM each), $MgCl_2$, 10 × PCR buffer (2 μl), dimethylsulfoxide (2 μl or zero, depending on PCR efficiency), PCR primers (20 pmol each), and Ex-Taq polymerase (2.5 U; Takara Tokyo, Japan). 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 55 or 60°C for 2 min, and extension at 72°C for 30 s.

Detection of SNPs and insertion/deletion polymorphisms

Fluorescent dye-terminator cycle sequencing (ABI PRISM Big Dye Terminator Cycle Sequencing Ready Reaction kit; PE Applied Biosystems) was performed using four primers for each amplified fragment (two for the forward side and two for the reverse side). Dye-terminated PCR amplifications were analyzed with an ABI 3700 autosequencer (PE Applied Biosystems). Detection of polymorphism was carried out using the PolyPhred computer program (Nickerson et al. 1997), which automatically detects the presence of heterozygous SNPs by fluorescence-based sequencing of PCR products (Ohnishi et al. 2000; Seki et al. 2000; Yamada et al. 2000; Iida et al. 2001). Allele frequencies were estimated individually by comparing the peak levels of signals among all 192 chromosomes.

Results and discussion

The human *NAT1* and *NAT2* genes are located on chromosome 8p22 (Blum et al. 1990), and share 81% nucleotide-sequence identity within their coding regions. However, the *NAT1* gene has a single exon, while *NAT2* consists of two

Table 1. Summary of polymorphic sites detected within the *NAT1* and *NAT2* genes

Gene	SNP no.	Location	Position[a]	SNP
NAT1	1	3′ Flanking	191–193	del.AAA[b]
	2	3′ Flanking	215	A/T[b]
	3	3′ Flanking	222	A/C[b]
NAT2	1	5′ Flanking	−2085	A/G[c]
	2	5′ Flanking	−2053	T/C
	3	5′ Flanking	−1299	A/G
	4	5′ Flanking	−1145	C/T
	5	5′ Flanking	−1036	T/A
	6	5′ Flanking	−843	A/G[c]
	7	5′ Flanking	−643	T/C
	8	5′ Flanking	−94	G/A
	9	Exon 2	288	C/T (Tyr94Tyr)
	10	Exon 2	347	T/C (Ile114Thr)[b]
	11	Exon 2	487	C/T[b]
	12	Exon 2	596	G/A (Arg197Gln)[b]
	13	Exon 2	809	A/G (Lys268Arg)[b]
	14	Exon 2	863	G/A (Gly286Glu)[b]
	15	3′ Flanking	521	G/A
	16	3′ Flanking	573	C/T
	17	3′ Flanking	918	A/G
	18	3′ Flanking	979	C/T
	19	3′ Flanking	1958	C/T
	20	3′ Flanking	2034	T/G
	21	3′ Flanking	2201	G/A
	22	3′ Flanking	2818	C/G
	23	3′ Flanking	3237	del.A
	24	3′ Flanking	3386	G/A
	25	3′ Flanking	3660	A/G
	26	3′ Flanking	3973	C/T
	27	3′ Flanking	4029	T/C
	28	3′ Flanking	4118	C/A
	29	3′ Flanking	4146	C/T
	30	3′ Flanking	4279	G/C
	31	3′ Flanking	4323	T/G
	32	3′ Flanking	4446	T/C
	33	3′ Flanking	4462	T/C

[a] For single-nucleotide polymorphisms (SNP) positions within the 3′ flanking region are counted from the 5′ end of the 3′ sequence; i.e., the 5′-most nucleotide of the 3′ flanking region is number 1. Within exons, nucleotide positions are counted from the first exonic nucleotide

[b] SNPs previously reported in the 'www.louisville.edu/medschool/pharmacology/NAT.html'

[c] SNPs previously reported in the dbSNP of GenBank

exons, one corresponding to the coding region and 3′ untranslated sequence, and the other corresponding to the 5′ untranslated region about 8kb upstream of the second exon. We identified 53 SNPs and two insertion/deletion polymorphisms by direct sequencing of DNA from 96 Japanese chromosomes. In the *NAT1* gene, which covers a 1.6-kb genomic region, two SNPs and a 3-bp insertion/deletion polymorphism were present in the 3′ untranslated region (Fig. 1A, Table 1). However, these polymorphisms were not novel; they were identical to variants reported elsewhere as NAT1*3, NAT1*10, NAT1*18A, and NAT1*18B alleles. Although 22 additional allelic variants of *NAT1* were identified previously (www.louisville.edu/medschool/pharmacology/NAT.html), we found only these 3 among our Japanese subjects. The frequencies of NAT1* alleles reported in Caucasians were 3% for NAT1*3, 16% for NAT1*10, 4.5% for NAT1*11, and 77% for NAT1*4 (rapid acetylator), as opposed to frequencies of 1.0% for NAT1*3, 40.6% for NAT1*10, 2.6% for NAT1*18A, 3.1% for NAT1*18B, and 52.6% for NAT1*4 in the Japanese population (Table 2). Although a large part of both ethnic groups consisted of NAT1*4 and NAT1*10, in terms of allele frequency, their frequencies are quite different. Furthermore, NAT1*11 was not identified in Japanese. In addi-

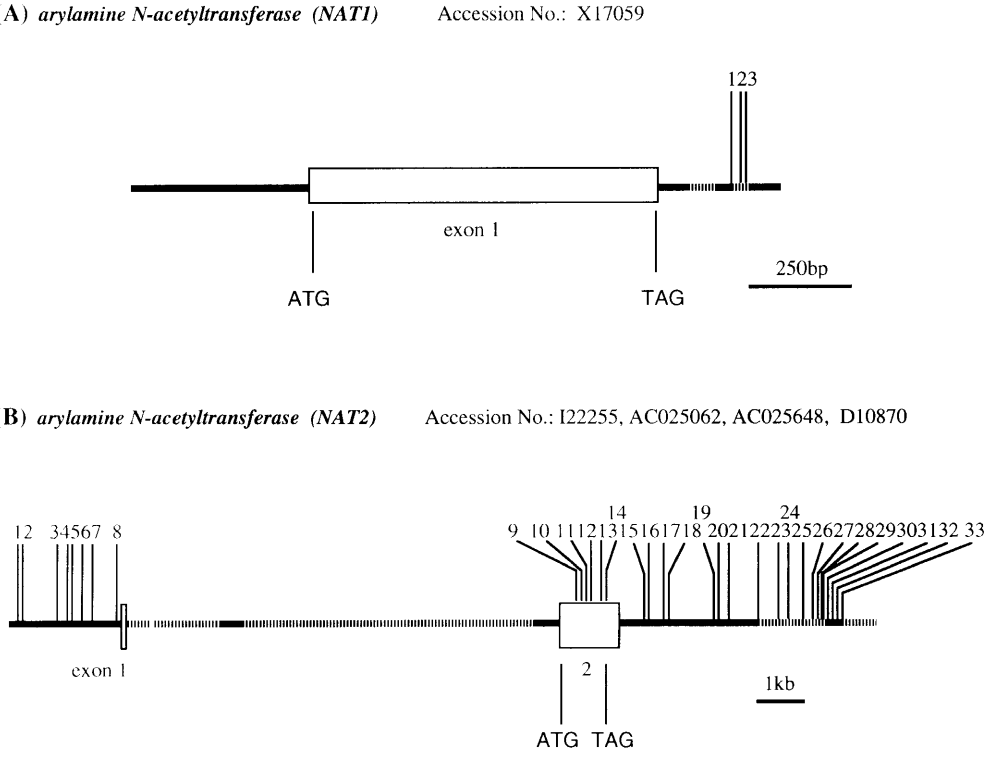

Fig. 1A,B. Locations of Single-nucleotide polymorphisms (SNPs) within **A** the *NAT1* and **B** *NAT2* genes, indicated by *vertical lines*. Each *number* above a vertical line corresponds to the appropriate SNP number in Table 1. *Open boxes* represent exons; *hatched lines* indicate regions of repetitive elements. *ATG* and *TAG*, initiation and stop codons, respectively

Table 2. *NAT1* and *NAT2* allele frequencies in the Japanese population

Allele[a]	Nucleotide changes(s)[b]	SNP no. in Table 1[c]	Amino acid change(s)	Type	Frequency[e]
NAT1*4	—	—	—	Rapid	52.6%
NAT1*3	C1095A	3	None	Unknown	1.0%
NAT1*10	T1088A, C1095A	2, 3	None	Unknown	40.6%
NAT1*18A	D3 between 1064–1067[d] T1088A, C1095A	1, 2, 3	None	Unknown	2.6%
NAT1*18B	D3 between 1064–1067[d]	1	None	Unknown	3.1%
NAT2*4	—	—	—	Rapid	51.3%
NAT2*5B	T341C, C481T, A803G	10, 11, 13	Ile114Thr, Lys268Arg	Slow	1.6%
NAT2*6A	C282T, G590A	9, 12	Arg197Gln	Slow	26.1%
NAT2*6B	G590A	12	Arg197Gln	Slow	2.2%
NAT2*7A	G875A	14	Gly286Glu	Slow	1.2%
NAT2*7B	C282T, G875A	9, 14	Gly286Glu	Slow	10.1%
NAT2*12A	A803G	13	Lys268Arg	Rapid	7.4%
NAT2*13	C282T	9	None	Rapid	1.1%

[a] Nomenclature of arylamine N-acetyltransferase is described in www.louisville.edu/medschool/pharmacology/NAT.html
[b] SNP positions are counted from the initiation codon
[c] Numbers correspond to SNP numbers in Table 1
[d] D3; 3-bp deletion
[e] Allele frequency was estimated individually, using 192 chromosomes from 96 Japanese healthy volunteers

tion, several rare NAT1* variants have also been reported in Caucasian groups. For example, the NAT1*14 variant (Arg187Gln) decreases stability of the protein and reduces its affinity for NAT1-selective substrates (Hughes et al. 1998). NAT1*15 (Arg187stop) and NAT1*19 (Arg33stop) proteins are truncated at about 90 and 240 amino acids from the carboxyl terminus, and NAT1*17 (Arg64Trp) and NAT1*22 (Asp251Val) proteins result in significant functional impairment of *NAT1* (Lin et al. 1998). The dichotomy between these reports and our results implies a difference between Japanese and Caucasian populations with regard to genotypes at the *NAT1* locus.

Within the *NAT2* gene, which encompasses a 17-kb genomic region, 32 SNPs and a 1-bp insertion/deletion polymorphism were identified (Fig. 1B); 6 SNPs were in the coding region, 8 were present in the 5′ flanking region, and 18 in the 3′ flanking region; the insertion/deletion polymorphism was in the 3′ flanking region. Four of the 6 SNPs in the coding region would cause amino-acid substitutions (Ile114Thr, Arg197Gln, Lys268Arg, and Gly286Glu); these six sites corresponded to alleles already designated NAT2*5B, *6A, *6B, *7A, *7B, and 12A. Two of the 8 SNPs in the 5′ flanking were reported in the dbSNP of GenBank. The remaining 24 SNPs and the insertion/deletion polymorphism we found in flanking regions were novel.

Genetic variations in *NAT2* have been shown to correlate with metabolic activities. A total of 13 SNP sites in the coding region have been reported to date, and nucleotide substitutions in each allele have been observed at a single site or at multiple sites. So far, 27 different polymorphic

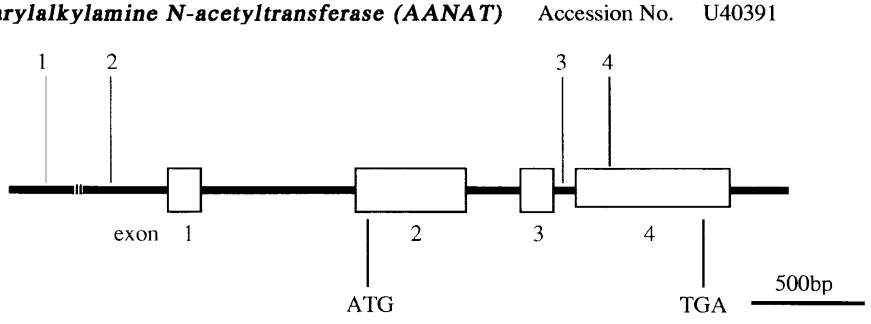

Fig. 2A–C. Locations of SNPs within **A** the *AANAT*, **B** *ARD1*, and **C** *L1CAM* genes, indicated by *vertical lines*. Each *number* above a vertical line corresponds to the SNP number in Table 3. *Open boxes* represent exons; *hatched lines* indicate regions of repetitive elements. *ATG* and *TAG* (*or TGA*), initiation and stop codons, respectively

sites have been reported (www.louisville.edu/medschool/pharmacology/NAT.html); among them, four clusters consisting of 19 alleles (NAT2*5, NAT2*6, NAT2*7, and NAT2*14) appear to confer slow acetylation. Amino-acid substitutions in NAT2*5 reduce the rate of substrate turnover, whereas in NAT2*6, NAT2*7, and NAT2*14 they reduce protein stability. Ethnic differences in allelic distribution have also been reported. In Caucasians, 17 allelic variants of the *NAT2* gene have been identified; in that population the rapid acetylator NAT2*4 is present at a lower frequency (21.6%) than slow acetylators (NAT2*5B, 41.6%; NAT2*6A, 23.6%; others, 5.5%) (Agundez et al. 1996). On the other hand, in the Japanese population, the rapid-type NAT2*4 was present at a higher frequency (51.3%) than the slow-type (NAT2*5B, 1.6%, NAT2*6A, 26.1%, NAT2*6B, 2.2%, NAT2*7A, 1.2%, NAT2*7B, 10.1%) (Table 2). These frequencies were similar to those reported by Okumura et al. (1997) (NAT2*4, 68.6%, NAT2*6A, 19.3%, NAT2*7B, 9.7%, NAT2*5B, 2.4%). We also identified rare *NAT2* variants, NAT2*6B and NAT2*7A, which had not been reported before in the Japanese population.

The human *AANAT* gene is located on chromosome 7q25 (Coon et al. 1996), and the *ARD1* and *L1CAM* genes are at Xq28 (Tribioli et al. 1994). Within the *AANAT* gene's 3.5-kb genomic region we discovered four SNPs, two in the 5′ flanking region, one in exon 4, and one in intron 3 (Fig. 2A, Table 3). In the 6.2-kb *ARD1* gene, nine SNPs were identified, all of them in introns (Fig. 2B, Table 3). In the 16-kb *L1CAM* gene, we found six intronic SNPs (Fig. 2C, Table 3). The genetic basis for variations among N-acetyltransferase genes may be associated with differences among individuals as regards the therapeutic efficacy and safety of drugs, and hormonal regulation.

Table 3. Summary of polymorphic sites detected within the *AANAT*, *ARD1*, and *L1CAM* genes

Gene	SNP no.	Location	Position[a]	SNP
AANAT	1	5′ Flanking	−542	G/T
	2	5′ Flanking	−263	C/G
	3	Intron 3	39	T/A
	4	Exon 4	150	C/T (Ala156Ala)
ARD1	1	Intron 1	317	G/C
	2	Intron 6	322	C/T
	3	Intron 6	394	A/G[b]
	4	Intron 6	1095	T/G
	5	Intron 6	1179	T/C
	6	Intron 7	159	G/A
	7	Intron 7	295	C/A
	8	Intron 7	416	T/C
	9	3′ UTR	47	C/T[b]
L1CAM	1	Intron 1	767	G/A
	2	Intron 1	862	G/C
	3	Intron 1	1332	C/T
	4	Intron 4	502	T/C
	5	Intron 18	147	C/A
	6	Intron 24	221	C/T

[a] For SNPs, positions within introns are counted from the first intronic nucleotide at the exon/intron junction. Within the 5′ flanking region, nucleotide positions are counted from the 3′ end of the 5′ sequence; i.e., the 3′-most nucleotide of the 5′ flanking region is number −1. Within the 3′ untranslated region (UTR), nucleotide position is counted from the first exonic nucleotide in the 3′ untranslated region. Within the exon, nucleotide position is counted from the first exonic nucleotide

[b] SNPs previously reported in the dbSNP of GenBank

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