Distribution of N-acetyltransferase Type 1 (NAT1) genotypes and alleles in a Turkish Population

Serdal Arslan, Naci Degerli and Fevzi Bardakci

Abstract

NAT1 is an intronless gene on chromosome 8p21.3 encoding a 290-amino-acid-long protein showing acetyltransferase activity. Some 26 alleles of NAT1 gene have been identified in human populations. In the present study we determined the distributions of NAT1 genotypes and alleles in a sample of 201 individuals from the Turkish population in Central Anatolia. The most frequent genotypes were NAT1*4/NAT1*4 (51.74%), NAT1*10/NAT1*4 (22.39%), NAT1*11/NAT1*4 (7.46), NAT1*10/NAT1*10 (3.98%). Frequencies of NAT1*3, *4 (wild-type), *10 and *11 alleles were 3.73%, 69.6%, 17.66% and 7.2%, respectively. The frequency of NAT1*11 was the highest amongst the populations studied so far, the other allele frequencies being close to those described in Caucasian populations.

Key words: NAT1 gene, genetic polymorphism, molecular epidemiology, Turkish population.

Received: July 4, 2003; Accepted: December 16, 2003.

...
assay was used to confirm the presence of allowing to distinguish a T (genotypes involving alleles not identifiable by SSCP analysis). The ten most frequent described genotypes, as well as eight rare alleles from the Turkish population is shown in Table 1. The PCR products were digested by Taq DNA polymerase (MBI Fermentas), 0.6 units and was performed on an 8% non-denaturing polyacrylamide gel, and the patterns analyzed after silver staining.

**PCR-RFLP Analysis of the NAT1 gene:** A RFLP-assay was used to confirm the presence of NAT1*11 alleles, allowing to distinguish a T (NAT1*4) from a G (NAT1*11) at the nucleotide 640, as described by Lo-Guidice et al. (2000). The PCR products were digested with AluNI (Fermentas). This enzyme cleaves NAT1*11 into three fragments (241, 451 and 496 bp), but other alleles into two fragments (451 and 746 bp). Therefore, restriction digestion produces three fragments (241, 451 and 496 bp) for NAT1*11/NAT1*11 genotype, and four fragments (241, 451, 496 bp and 746 bp) for NAT1*11/any other allele genotypes.

The NAT1 genotype distribution of the 201 individuals from the Turkish population is shown in Table 1. The ten most frequent described genotypes, as well as eight rare genotypes involving alleles not identifiable by SSCP analysis were found: NAT1*4/NAT1*4 (53.89%), NAT1*4/NAT1*10 (22.39%) and NAT1*4/NAT1*11 (7.46%) were the most common ones. The frequencies of the different alleles are shown in Table 2. The wild-type allele NAT1*4 had a frequency of 69.65%. The frequencies of NAT1*10, *11, *3 and of the non-identifiable alleles were 17.41%, 7.21%, 3.73% and 2%, respectively.

The frequencies of NAT1*3, NAT1*4 and NAT1*10 alleles observed were close to those found in German (Henning et al., 1999), Canadian (Hughes et al., 1998), and French (Lo-Guidice et al., 2000) populations. A striking difference in the Turkish population was the highest NAT1*11 frequency (7.2%). Although this allele was not found in the French population (Lo-Guidice et al., 2000), it has been reported with a lower frequency in German (2.7% by Henning et al., 1999 and 3.3% by Bruhn et al. 1999) and in Canadian (2.1% by Hughes et al., 1998) populations. These populations differ from the Japanese who present the NAT1*10 allele as the most frequent, and among whom NAT1*3 and *11 alleles were never found (Yang et al., 2000). In Indian, Malay and Chinese populations, Zhao et al. (1998) reported a much higher NAT1*10 and NAT1*3 allele frequencies than those found in Caucasians.

**Table 1:** Distribution of observed and expected numbers of NAT1 genotypes in a sample from the Turkish population.

<table>
<thead>
<tr>
<th>Genotypes</th>
<th>Number of individuals</th>
</tr>
</thead>
<tbody>
<tr>
<td>Observed</td>
<td>Expected</td>
</tr>
<tr>
<td>NAT1<em>3/NAT1</em>3</td>
<td>2</td>
</tr>
<tr>
<td>NAT1<em>3/NAT1</em>4</td>
<td>4</td>
</tr>
<tr>
<td>NAT1<em>4/NAT1</em>4</td>
<td>104</td>
</tr>
<tr>
<td>NAT1<em>10/NAT1</em>3</td>
<td>5</td>
</tr>
<tr>
<td>NAT1<em>10/NAT1</em>4</td>
<td>45</td>
</tr>
<tr>
<td>NAT1<em>10/NAT1</em>10</td>
<td>8</td>
</tr>
<tr>
<td>NAT1<em>11/NAT1</em>3</td>
<td>2</td>
</tr>
<tr>
<td>NAT1<em>11/NAT1</em>4</td>
<td>15</td>
</tr>
<tr>
<td>NAT1<em>11/NAT1</em>10</td>
<td>4</td>
</tr>
<tr>
<td>NAT1<em>11/NAT1</em>11</td>
<td>4</td>
</tr>
<tr>
<td>NAT1*4/other</td>
<td>8</td>
</tr>
<tr>
<td>NAT1*5/other</td>
<td>0</td>
</tr>
<tr>
<td>NAT1*10/other</td>
<td>0</td>
</tr>
<tr>
<td>NAT1*11/other</td>
<td>0</td>
</tr>
</tbody>
</table>

A small departure (significant at the 5% level) from Hardy-Weinberg genotype proportions was observed (chi-squared = 12.31; d.f. = 4; p = 0.015). Only the deficiency of NAT1*3/NAT1*4 heterozygotes seems to contribute significantly to the obtained chi-squared figure. Both the sample size and its heterogeneous ethnic composition are the best explanation for this finding.

Yang et al. (2000) reported a higher activity of the enzyme encoded by NAT1*10 allele in a Japanese population, with NAT1*4/NAT1*10 female heterozygotes having higher enzyme activity than NAT1*4/NAT1*4 females. Wikman et al., (2001) considered individuals with NAT1*10 allele as rapid acetylators unless when combined with a slow allele. In contrast, Bruhn et al. (1999) did not detect increased enzyme activities in association with NAT1*4/*4, NAT1*4/*10 and NAT1*10/*10 genotypes in a German population. Jourenkova-Mironova et al. (1999) have also found low frequencies of NAT1 homozygous rapid acetylator genotypes (NAT1*10/*11 and NAT1*10/*10). Associations between the NAT1*10 allele and a high enzyme activity with oral (Katoh et al., 1998), colon (Bell et al., 1995b), urinary bladder (Taylor et al., 1995), head and neck (Olshan et al., 2000) and gastric (Katoh et al., 1995b) cancers.

**Table 2:** Frequencies of NAT1 alleles in a sample from the Turkish population.

<table>
<thead>
<tr>
<th>Alleles</th>
<th>Mutations</th>
<th>N. of alleles (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>NAT1*3</td>
<td>1095C &gt; A</td>
<td>15 (3.73)</td>
</tr>
<tr>
<td>NAT1*4</td>
<td>Wild-type</td>
<td>279 (69.65)</td>
</tr>
<tr>
<td>NAT1*10</td>
<td>1088T &gt; A, 1095C &gt; A</td>
<td>71 (17.41)</td>
</tr>
<tr>
<td>Others</td>
<td></td>
<td>8 (1.99)</td>
</tr>
</tbody>
</table>
2000) cancers have been described. In addition, linkage
disequilibrium between NAT1*10 and NAT2 alleles has
been reported in a German population, with half of the
NAT1*10 alleles being linked to mutant NAT2 alleles
(Henning et al., 1999). NAT1*11 allele, with the highest
frequency reported thus far in the Turkish population, has
been considered as a putative rapid allele in Caucasians and
Black South Africans (Zheng et al. 1999; Lcktionov et al.
2002). A possibility deserving investigation is of an associ-
ation between NAT1*11 allele and certain cancers as shown
for NAT1*10, another rapid acetylator.

Acknowledgments
This work was supported by grants from the Sci-
centific Research Fund of Cumhuriyet University, Sivas to
Fevzi Bardakci (Grant n. F-122).

References
Bell DA, Badawi AF, Lang NP, Ilett KF, Kadlubar FF and Hir-
vonen A (1995a) Polymorphism in the N-acetyltransferase 1
(NAT1) polyadenylation signal: association of NAT1*10
allele with higher N-acetylation activity in bladder and colon
Bell DA, Stephens EA, Castranio T, Umbach DM, Watson M,
Deakin M, Elder J, Hendrickse C, Duncan H and Strange RC
(1995b) Polyadenylation polymorphism in the acetyltrans-
erase 1 gene (NAT1) increases risk for colorectal cancer.
Bruhn C, Brockmoller J, Cascorbi I, Roots I and Borchester HH
(1999) Correlation between genotype and phenotype of the
human arylamine N-Acetyltransferase Type 1 (NAT1). Biochem Pharmacol 58:1759-1764.
Butcher NJ, Ilett KF and Minchin RF (1998) Functional polymor-
phism of the human arylamine N-acetyltransferase type 1
gene caused by C190T and G560A mutations. Pharma-
cogenetics 8:67-72.
Deguchi T, Mashimo M and Suzuki T (1990) Correlation between
acetyltransferase phenotypes and genotypes of polymorphic aryl-
naturally occurring and recombinant human N-acetyl-
transferase-1 gene variants encoded by NAT1*. Mol Phar-
cacol 58:288-299.
polymorphism of human arylamine N-acetyltransferase
NAT1 using p-aminosalicylic acid as an in vivo probe. J Bas-
ic Clin Physiol Pharmacol 3(suppl.4):244.
Hein DW, Grant DM and Sim E (2000) Update on consensus
arylamine N-acetyltransferase gene nomenclature. Pharma-
cogenetics 10:291-292.
Association of arylamine N-acetyltransferases NAT1 and
NAT2 genotypes to laryngeal cancer risk. Pharmacogenetics
9:103-111.
Hughes NC, Janezic SA, MacQuen KL, Jewett MAS, Castranio T,
Bell DA and Grund DM (1998) Identification and character-
zation of variant alleles of human N-acetyltransferase NAT1

Jourenkova-Mironova N, Wikman H, Bouchardy C, Mitrunen K,
Dayer P, Benhamous S and Hyvonen A (1999) Role of
arylamine N-acetyltransferase 1 and 2 (NAT1 and NAT2) ge-
notypes in susceptibility to oral/pharyngeal and laryngeal
Katoh T, Boissy R, Nagata N, Kitagawa K, Kuroda Y, Itoh H,
Kawamoto T and Bell DA (2000) Inherited polymorphism in
the N-acetyltransferase 1 (NAT1) and 2 (NAT2) genes and
susceptibility to gastric and colorectal adenocarcinoma. Int J
Cancer 85:46-49.
Katoh T, Kaneko S, Boissy R, Watson M, Ikemura K and Bell DA
(1998) A pilot study testing the association between N-
acetyltransferases 1 and 2 and risk of oral squamous cell car-
Lin HJ, Probst-Hensch NM, Hughes NC, Sakamoto GT, Louie AD,
N-acetyltransferase NAT1 and a case-control study of cole-
Lo-Guidice J-M, Allorge D, Chevalier D, Herve D, Fazio F,
Lafitte JY and Broly F (2000) Molecular analysis of the
N-acetyltransferase 1 (NAT1) using polymerase chain reac-
tion-restriction-fragment single strand conformation poly-
morphism assay. Pharmacogenetics 10:293-300.
Loktionov A, Moore W, Spencer SP, Vorster H, Neill T, O’Neill
IK, Bringham SA and Cummings JH (2002) Differences in
N-acetylation genotypes between Caucasians and Black
South Africans: implications for cancer prevention. Cancer
Detect Prev 26:15-22.
Olahan AF, Wieswiler M, Watson MA and Bell DA (2000)
GSTM1, GSTT1, GSTP1, CYP1A1, and NAT1 polymor-
Taylor JA, Umbach D, Stephan E, Paulson D, Robertson C,
Mohler JL and Bell DA (1995) Role of the N-acetylation
polymorphism at NAT1 and NAT2 in smoking-associated
Vatsis KP and Weber WW (1993) Structural heterogeneity of
Caucasian N-acetyltransferase at the NAT1 gene locus. Arch
Biochem Biophys 301:71-76.
L, Diemennam H, Kayser K, Schulz V, Drings P, Bartsch H
and Risch A (2001) Relevance of N-acetyltransferase 1 and
2 (NAT1, NAT2) genetic polymorphisms in non small cell
Yang M, Katoh T, Delongchamp R, Ozowa S, Kohshi K and
Kawamoto T (2000) Relationship between NAT1 genotype
and phenotype in a Japanese population. Pharmacogenetics
Zenser TV, Lakshmi VM, Rustan TD, Doll MA, Deitz AC, Davis
BB and Hein DW (1996) Human N-acetylation of benzi-
Zhao B, Lee EJ, Yeoh PN and Gong NH (1998) Detection of mu-
tations and polymorphism of N-acetyltransferase 1 and 2
in the NAT1 and NAT2 genes in non small cell
Zheng W, Dietz A, Chambell D, Wen W-Q, Cerhan J, Sellers T,
Folsom A and Hein DW (1999) N-Acetyltransferase 1 ge-
netic polymorphism, cigarette smoking, well-done meat in-
take, and breast cancer risk. Cancer Epidemiol Biomarkers
Prev 8:233-239.

Editor Associado: Francisco Mauro Salzano