

## Gene Section

### Mini Review

# NAT2 (N-acetyltransferase 2 (arylamine N-acetyltransferase))

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Published in Atlas Database: January 2009

Online updated version : <http://AtlasGeneticsOncology.org/Genes/NAT2ID41498ch8p22.html>

DOI: 10.4267/2042/44640

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## Identity

**Other names:** AAC2; PNAT

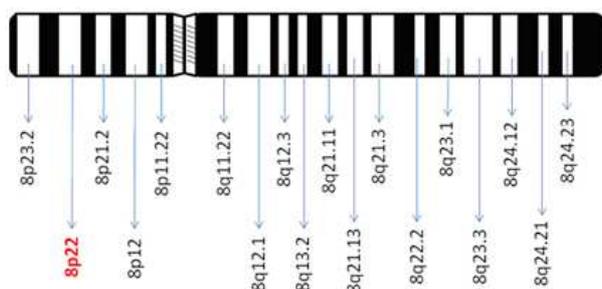
**HGNC (Hugo):** NAT2

**Location:** 8p22

### Note

In humans NAT2 is located in the NAT cluster that comprises 230 kb and includes two functional genes, NAT1 and NAT2.

In other species the number of NAT genes range from 0, for instance in dogs, to 4 for instance in chicken.



Picture from Genetics Home Reference; January 2009.

## DNA/RNA

### Transcription

The human NAT2 gene has two exons but the coding region, spanning 870 bp is located in exon 2. Functionally active NAT2 enzyme can be obtained after transient heterologous transfection of

the open reading frame only, indicating that exon 1 is not necessary to obtain functional enzyme.

### Pseudogene

In humans the NAT locus has a pseudogene designated as NATP.

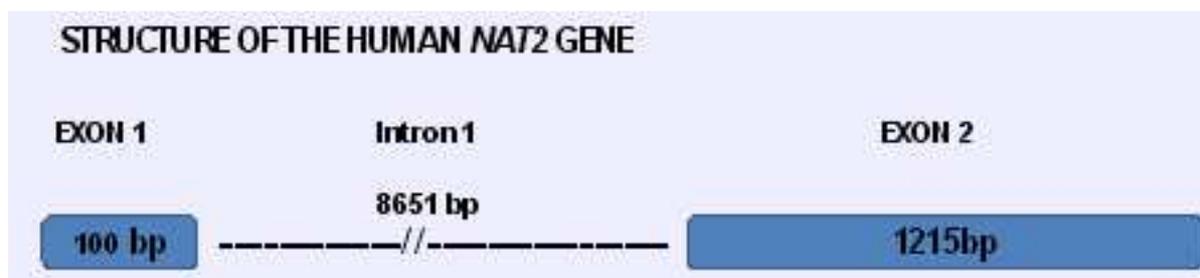
## Protein

### Note

NAT enzymes have been identified in several vertebrate and microorganism species. NAT2 proteins differ among species. However, common features include an 83 amino acid N-terminal domain containing five alpha-helices and a short beta-strand; a second domain consisting of nine beta-strands and two short helices; and a third alpha/beta lid domain with four beta-strands and an alpha-helix.

### Expression

NAT2 has a restricted expression profile with the highest levels of protein and mRNA being detected in the liver, small intestine and colon. The transcription start site for human NAT2 has been recently localised between 30 and 101 bp upstream of the non-coding exon, with the most frequent TSS located at position -64 relative to exon 1. The region containing the NAT2 transcription start site shares an 85% sequence homology to the region of human NAT1 containing the major transcription start site for NAT1. The functional elements of the NAT2 promoter sequence have not been characterised to date.



### Localisation

Arylamine *N*-acetyltransferase 2 is a cytosolic enzyme.

### Function

NAT2 is a phase II enzyme that participates in the metabolism of numerous primary arylamines and hydrazine drugs and carcinogens. In addition to their *N*-acetylation catalytic activity, NAT enzymes have also *O*-acetylation activity towards *N*-hydroxyarylamines.

### Homology

NAT1 and NAT2 share 87% nucleotide homology in the coding region, whereas NAT1 and NAT2 proteins share 81% amino-acid sequence identity.

## Mutations

### Note

Seven major single nucleotide polymorphisms that occur isolated or combined have been described in the NAT2 gene. These affect the positions 191, 282, 341, 481, 590, 803 and 857. In addition, rare SNPs affecting the positions 111, 190, 364, 411, 434, 499, 795, 845 and 859 have been described although their frequencies are unknown. For details on NAT2 SNPs and haplotypes, see <http://louisville.edu/medschool/pharmacology/Human.NAT2.pdf>. Critical gene variants leading to slow acetylation capacity contains mutations at positions 191, 341, 590 or 857. Since some genotypes can be due to the presence of different combinations of haplotypes leading to ambiguous phenotype prediction, haplotype reconstruction is often necessary to clarify ambiguous genotype data.

## Implicated in

### Note

Determination of the NAT2 genotype or phenotype has been proposed to predict adverse reactions in patients

with tuberculosis receiving isoniazid, prior to the concomitant administration of drug combinations such as procainamide-phenytoin or doxyciline-rifampin. In addition, several human diseases have been related to NAT2 polymorphism. There are described below.

### Brain cancer

#### Prognosis

Preliminary findings argue for association of a trend towards higher risk in individuals classified as NAT2 homozygous rapid acetylators in patients with astrocytoma or meningioma.

### Lung cancer

#### Prognosis

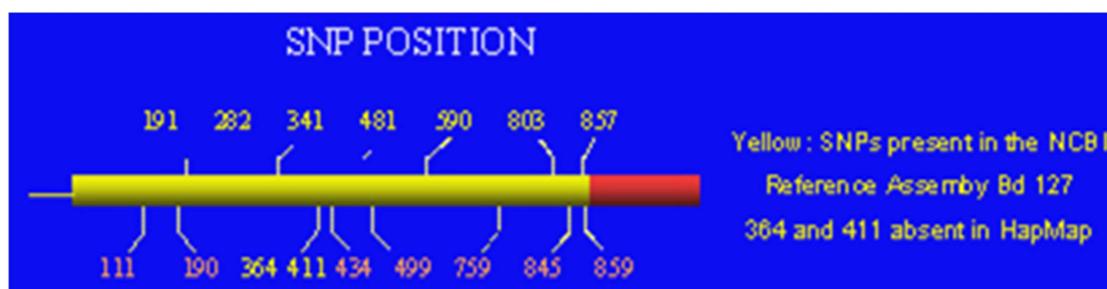
Several studies based on an initial hypothesis that slow acetylation may increase the risk of developing lung cancer have been conducted.

This hypothesis has been reinforced by studies indicating that slow acetylation, especially if it is associated to defect genotypes for other phase II enzymes, may confer increased susceptibility to the formation of adducts. Several studies have concluded that the NAT2 slow acetylation genotype causes a marginally increased risk of developing lung cancer. In spite of these findings, present evidence suggests that the NAT2 polymorphism alone does not constitute a relevant risk factor for lung cancer. However this polymorphism may reinforce the effect of other genetic and/or environmental factors.

### Liver cancer

#### Prognosis

A role for xenobiotic-metabolising enzymes in liver carcinogenesis is to be expected among patients with environmentally-related liver cancer since, besides viral hepatitis, liver cancer may be related to environmental substances. The findings obtained in patients with primary liver cancer not related to viral hepatitis are consistent and indicate a minor, but relevant, association of the slow NAT2 acetylation status and predisposition to liver cancer.



## Colorectal cancer

### Prognosis

The hypothesis that acetylator status may predispose to a determined cancer risk is based on a differential effect of N-acetylation as a potential detoxification step and O-acetylation as a potential carcinogen-activation step. In the case of colorectal cancer it was hypothesized that O-acetylation is more relevant than N-acetylation, and therefore the rapid acetylation genotype is the putative risk status associated with colorectal cancer. Sufficient evidence is available to rule out a relevant association of NAT genotypes alone with colorectal cancer risk. However, the putative interaction of meat consumption and the NAT2 genotype deserves particular attention.

## Bladder cancer

### Prognosis

Despite the large number of studies and meta-analyses performed in several human populations, current evidence is not sufficient to confirm unambiguously an association of NAT2 polymorphism to overall bladder cancer risk. A general association of the slow acetylation status with bladder cancer risk has not been fully confirmed, although meta-analyses have obtained positive findings for a modest association of the slow NAT2 acetylation genotype with bladder cancer risk, with odds ratio values between 1.3 and 1.5. Furthermore, the biological basis for the putative association is uncertain. In diverse independent studies, mutagenicity in urine was tested in individuals exposed to urban pollution, smoking, red meat intake or textile dyes. In all cases, no higher mutagenicity in slow NAT2 acetylators could be established when compared to these or rapid acetylators, and in fact among individuals exposed to urban pollution, rapid acetylators showed a higher mutagenicity in urine than slow acetylators. In a study investigating the influence of NAT genotypes in the association between permanent hair dyes and bladder cancer, a significant association of the slow NAT2 acetylation genotype was identified. However these findings could not be replicated in other studies.

## Breast cancer

### Prognosis

After dozens of studies involving several thousands of

breast cancer patients, as well as meta-analyses, today it is obvious that no major association of NAT2 polymorphism and breast cancer risk exists.

## Head and neck cancer

### Prognosis

Since chemical compounds present in tobacco are inactivated by phase II enzymes, it has been proposed that head and neck cancer risk could be modified by NAT genotypes. However, overall findings indicate that no relevant association between NAT2 polymorphism and head and neck cancer risk is to be expected.

## Other diseases

### Disease

Although a relation of risk may be definitely discarded for systemic lupus erythematosus (SLE), inflammatory bowel disease and endometriosis, more research is needed for rheumatoid arthritis, Parkinson's, Alzheimer's, Behçet's and periodontal diseases, as current results are inconclusive but suggest a possible relation with NAT2 polymorphism. In diabetes mellitus the possible relation with the rapid phenotype may be due to acquired metabolic changes and more genotyping studies are needed. NAT2 slow metabolizers are more prone to the side effects of polymorphically acetylated drugs, as is the SLE-like syndrome induced by hydralazine and procainamide, the side effects due to sulphasalazine and the skin rash secondary to many sulphonamides.

## To be noted

### Note

Large interethnic and intraethnic variability exists in the frequency for common SNPs at the NAT2 gene. Future association studies should take into consideration such differences and ambiguous NAT2 genotypes.

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*This article should be referenced as such:*

Ruiz JD, Agúndez JAG, Martínez C, García-Martín E. NAT2 (N-acetyltransferase 2 (arylamine N-acetyltransferase)). *Atlas Genet Cytogenet Oncol Haematol*. 2009; 13(12):952-955.

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