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Gene Section
Review

NAT1 (N-acetyltransferase 1 (arylamine N-acetyltransferase))

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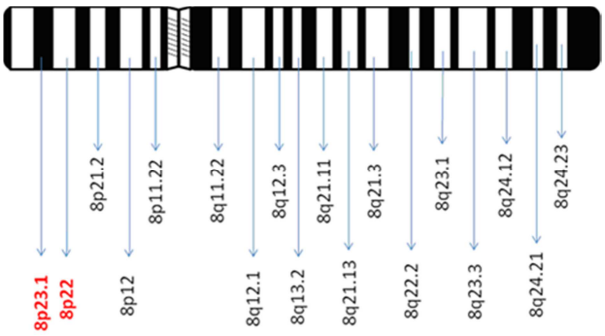
Identity

Other names: AAC1; MNAT

HGNC (Hugo): NAT1

Location: 8p22



Picture adapted from an original prepared by Genetics Home Reference; February 2009.

DNA/RNA

Note

In humans NAT1 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 to 4.

Transcription

The human NAT1 gene has nine exons. The coding region is located in exon 9 and spans 870 bp. Diverse NAT1 transcripts have been reported and two promoters exist. The first promoter, designated as P1 is located in the 5' flanking region of exon 1 and controls two major (a1 and a2) transcripts. The second promoter is located upstream of exon 4 and give rise to at least five (b1 to b5) different transcripts. The different transcripts appear to have different translational efficiencies, although the biological significance of this is unknown (revised in Butcher et al., 2007).

Pseudogene

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

Protein

Note

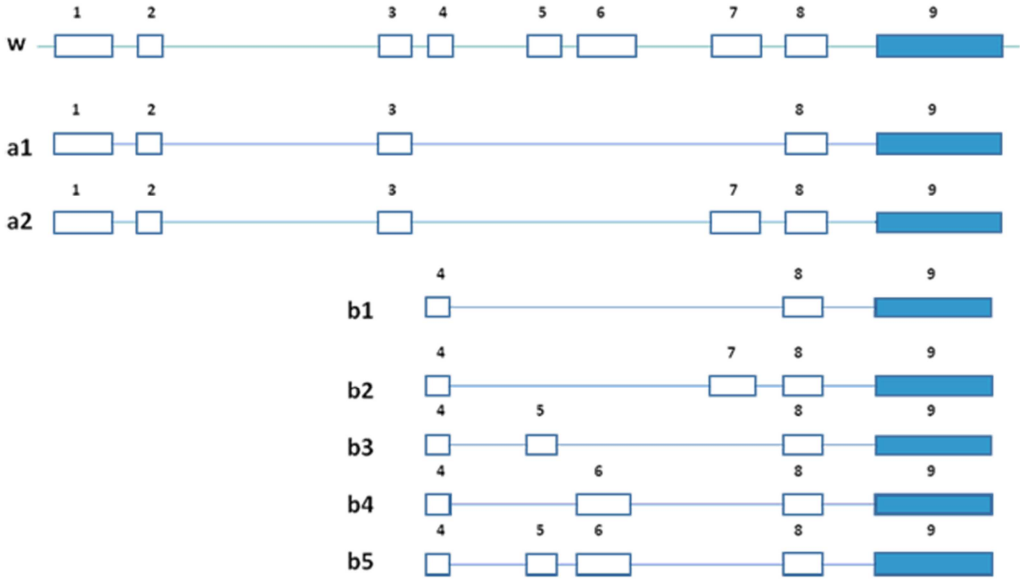
NAT enzymes have been identified in several vertebrate and microorganism species, whereas NAT deficiency in the domestic and wild dog is due to complete absence of NAT genes.

Description

The amino-terminal domain (residues 1-83) consists of five helices and one short beta-strand. The second domain comprises residues 85-192 and consists of nine beta-strands and two short helices. The third domain has a final helix which precedes the carboxy terminal region.

Expression

NAT1 activity is expressed in liver and in many extrahepatic tissues. The transcripts originated from the first promoter, NATa, are expressed in kidney, liver, lung and trachea. However the most common transcripts are those designated as type b in the



Structure of the human NAT1 gene and common NAT1 transcripts.

Figure above and have been detected in all tissues examinated.

Localisation

Arylamine N-acetyltransferases are cytosolic enzymes.

Function

NAT1 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

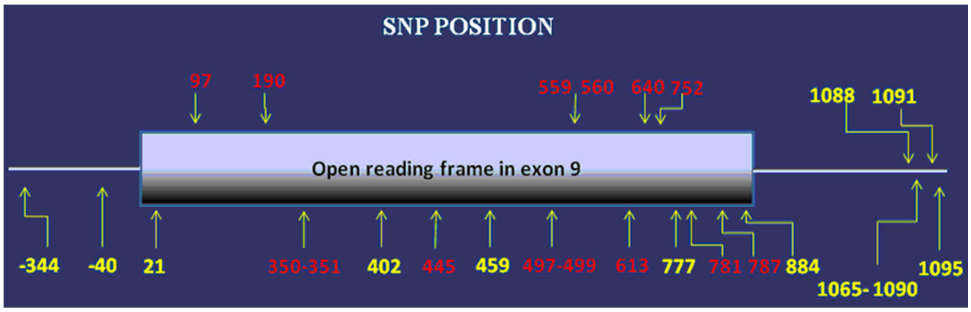
In humans NAT1 is highly polymorphic. Several polymorphisms, most of which are single nucleotide polymorphisms and at least 26 different haplotypes have been described. The Figure below shows the positions of NAT1 polymorphisms, taking as a reference the start site in the open reading frame (ORF) in exon 9. Nonsynonymous polymorphisms are labeled in red font. The association of different haplotypes with phenotypes is summarized in the following link: http://louisville.edu/medschool/pharmacology/Human.NAT1.pdf.

Implicated in

Lung cancer

Note

Two independent studies have observed a significant association of the NAT1 polymorphism with lung cancer risk (Bouchardy et al., 1998; Wikman et al., 2001). However these studies should be interpreted cautiously because these do not agree on the NAT1 risk genotype. Another study identified an increased risk among carriers of NAT1 plus NAT2 slow genotypes (Gemignani et al., 2007). In a meta-analysis carried out with smokers that suffered from non small-cell lung cancer a relevant association of the NAT1 rapid acetylation genotype was identified (Zienolddiny et al., 2008). Although negative associations have been reported (Perera et al., 2006), NAT1 is emerging as the NAT gene most likely related to lung cancer (McKay et al, 2008).



Head and neck cancer

Note

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. Head and neck cancers are strongly associated with smoking, and a few studies have explored the role of NAT1 polymorphisms in the risk of developing head and neck cancer in smokers. However overall findings are inconsistent and associations if present are weak, and indicate either a decreased risk in carriers of the variant NAT1*10 (McKay et al., 2008), an increased risk (Katoh et al., 1998) or a lack of association (Fronhoffs et al., 2001; Henning et al., 1999; Agúndez, 2008).

Breast cancer

Note

The NAT1*10 variant allele was associated to increased breast cancer risk among women who consumed well-done meat, although the statistical significance of this finding is low (Krajinovic et al., 2001). Several studies, however, indicate that no major association of NAT polymorphisms and breast cancer risk exists (Agúndez, 2008).

Colorectal cancer

Note

A biologically plausible mechanistic hypothesis suggest that rapid NAT1 and/or NAT2 acetylators should more activate heterocyclic amine carcinogens within the colon to their ultimate carcinogenic forms, thereby predisposing them to colorectal cancer. However sufficient evidence is available to rule out a relevant association of NAT genotypes alone with colorectal cancer risk. This evidence is based in nearly thirty studies failed to detect a statistically significant association for NAT1 genotypes both with colorectal cancer or adenomas. In addition meta-analyses (Chen et al., 2005; Ye et al., 2002; Houlston et al., 2001) consistently confirm a lack of a relevant association of NAT1 rapid acetylator genotypes and colorectal cancer risk (revised in Agúndez, 2008).

Bladder cancer

Note

No significant association of the NAT1 genotype with bladder cancer risk has been observed in a recent meta-analysis, although the authors found a joint effect of NAT1 rapid genotypes, slow NAT2 genotypes and smoking as factors increasing cancer risk (Sanderson et al., 2007). Overall findings are negative (Okkels et al., 1997), although a significant risk has been described in smokers (Taylor et al., 1998; Hsieh et al., 1999; Cascorbi et al., 2001) and a nearly significant association was observed in individuals exposed to benzidine (Carreon et al., 2006).

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