



## Isoniazid Inactivation

### Alternative Names

INH Inactivation  
N-Acetyltransferase Polymorphism  
Acetylator Phenotype  
Arylamine N-Acetyltransferase 2  
NAT2  
Arylamide Acetylase 2  
AAC2

### OMIM Number

243400

### Mode of Inheritance

Autosomal Recessive

### Gene Map Locus

8p23.1-p21.3

### Description

The N-acetylation of arylamines and acetoxy esters, a process carried out by the enzyme N-acetyltransferase, is considered to be a major detoxification step of the arylamine carcinogens in humans. N-acetyltransferase is functionally expressed by two polymorphic isoenzymes: N-acetyltransferase 1 and N-acetyltransferase 2.

N-acetyltransferase 2 is an enzyme that functions to both activate and deactivate arylamine and hydrazine drugs and carcinogens. Polymorphisms in this gene are responsible for the N-acetylation polymorphism in which human populations segregate into rapid, intermediate and slow acetylator phenotypes. Genetic polymorphism of N-acetyltransferase 2 is related with the susceptibility towards various malignant tumors, such as bladder cancer, lung cancer, and colorectal cancer.

### Molecular Genetics

The intronless N-acetyltransferase 2 gene maps on chromosome 8, at 8p22, covering 9.97 kb on the direct strand. Its protein has 290 amino acids (33.5 kDa), contains one N-acetyltransferase domain, and has a cytoplasmic sub-cellular

location. Three major slow acetylator NAT2 alleles have been identified, and the number of minor, rare NAT2 alleles is to date greater than 30. NAT2\*4 has traditionally been designated the "wild type" human N-acetyltransferase 2 allele. It is the most common occurring allele in some, but not all ethnic groups.

### Epidemiology in the Arab World

#### Egypt

Hashem et al. (1969) reported that Egyptians have the highest incidence of the slow-acetylator phenotype (92%). In 2003, Hamdy et al., studied the frequencies of important allelic variants in the N-acetyltransferase 2 gene in a sample of 200 unrelated Egyptian subjects and compared them with the frequencies in other ethnic populations. N-acetyltransferase 2 gene variants (\*5,\*6 and \*7) were detected using an allele-specific real-time PCR assay. Genotyping of the N-acetyltransferase 2 gene revealed frequencies of 0.215, 0.497, 0.260 and 0.028 for \*4 (wild-type), \*5 (341C), \*6 (590A) and \*7 (857A), respectively. Hamdy et al. (2003) found that Egyptians resemble other Caucasians with regard to allelic frequencies of the tested variants of the N-acetyltransferase 2 gene. However, the predominance of the slow acetylator genotype in their study (60.50%) could not confirm the frequency previously reported by Hashem et al. (1969), indicating the possibility of the presence of other mutations not detectable as T341C, G590A and G857A.

#### Saudi Arabia

El-Yazigi et al. (1989) examined acetylator phenotypes of 296 Saudi subjects of Arabic origin by measuring the molar concentration ratio of two caffeine metabolites, 5-acetylamino-6-formylamino-3-methyluracil (AFMU) and 1-methylxanthine (1MX). The subjects were originally from different regions of Saudi Arabia but, at the time of the study,



lived primarily in the capital city of Riyadh. The day-to-day reproducibility of the molar concentration ratio of AFMU/1MX was established in 14 randomly selected subjects. These metabolites were stable in urine at 4 degrees and -20 degrees, but AFMU was unstable at room temperature (23 degrees). The frequency distribution data indicate that 72.3% (ranging from 65-90%) of the subjects are of slow acetylator phenotype.

#### **Tunisia**

Attitallah et al. (2000) compared the acetylation status in the three main racial/ethnic groups living in Tunisia: Arabs, Berbers and Numides. The frequency of slow acetylators appears identical in these three groups and is different from that observed in Caucasians. However, the N-acetyltransferase type 2 activity as a whole is lower in Tunisians than in Caucasians. Attitallah et al. (2000) attributed these differences to the various population mixings which occurred in the past, given the geographical position of Tunisia.

#### **United Arab Emirates**

In year 1996, Bastaki et al. studied the distribution of polymorphic N-acetyltransferase (NAT2) phenotypes in 118 unrelated, apparently healthy, Emirati schoolboys in the eastern region of Abu Dhabi. Phenotypes were assigned by determination of the 5-acetylamino-6-formylamino-3-methyluracil/1-methylxanthine (AFMU/1X) urinary molar excretion ratio after oral ingestion of caffeine.

The results of this study indicated a prevalence of the slow acetylator phenotype among United Arab Emirate nationals of 61%. The fast acetylator phenotype included many individuals with intermediate acetylating capacity that could be cautiously identified as heterozygotes.

#### **References**

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