MAYO CLINIC LABORATORIES

Test Definition: NAT2Q

N-Acetyltransferase 2 (NAT2) Genotype, Varies

Overview

Useful For

Identifying patients who may be at risk for altered metabolism of drugs that are substrates of arylamine *N*-acetyltransferase type 2 (NAT2), including isoniazid

Special Instructions

- Informed Consent for Genetic Testing
- Pharmacogenomic Association Tables
- Multiple Genotype Test List
- Informed Consent for Genetic Testing (Spanish)

Method Name

Real-Time Polymerase Chain Reaction (PCR) with Allelic Discrimination Analysis

NY State Available

Yes

Specimen

Specimen Type

Varies

Specimen Required

Multiple genotype tests can be performed on a single specimen after a single extraction. See Multiple Genotype Test List for a list of tests that can be ordered together.

Submit only 1 of the following specimens:

Specimen Type: Whole blood
Container/Tube: Lavender top (EDTA)
Specimen Volume: 3 mL
Collection Instructions:
1. Invert several times to mix blood.
2. Send whole blood specimen in original tube. **Do not aliquot.**
Specimen Stability Information: Ambient (preferred) 9 days/Refrigerated 30 days

Specimen Type: Saliva
Patient Preparation: Patient should not eat, drink, smoke, or chew gum 30 minutes prior to collection.
Supplies: Saliva Swab Collection Kit (T786)
Specimen Volume: 1 Swab

Collection Instructions: Collect and send specimen per kit instructions.
Specimen Stability Information: Ambient 30 days

Specimen Type: Extracted DNA
Container/Tube: 2 mL screw top tube
Specimen Volume: 100 mcL (microliters)
Collection Instructions:
1. The preferred volume is 100 mcL at a concentration of 50 ng/mcL.
2. Include concentration and volume on tube.
Specimen Stability Information: Frozen (preferred)/Ambient/Refrigerated

Forms

1. **New York Clients-Informed consent is required.** Document on the request form or electronic order that a copy is on file. The following documents are available:
-Informed Consent for Genetic Testing (T576)
-Informed Consent for Genetic Testing-Spanish (T826)
2. If not ordering electronically, complete, print, and send 1 of the following with the specimen:
-Neurology Specialty Testing Client Test Request (T732)
-Therapeutics Test Request (T831)

Specimen Minimum Volume

Blood: 0.4 mL
Saliva: 1 swab

Reject Due To

All specimens will be evaluated at Mayo Clinic Laboratories for test suitability.

Specimen Stability Information

Specimen Type	Temperature	Time	Special Container
Varies	Varies		

Clinical & Interpretive

Clinical Information

Arylamine *N*-acetyltransferase type 2 (NAT2) is a highly polymorphic phase 2 metabolic enzyme that conjugates hydrazine derivatives and aromatic amine drugs with acetyl-groups.(1) NAT2 also is involved in the acetylation and activation of some procarcinogens.(1,2)

Individuals acetylate drugs at different rates by NAT2 and are described as having slow, intermediate, or rapid (fast) acetylator phenotypes. Some studies, which have examined diversity of *NAT2* haplotypes among individuals of different ethnicities hypothesize that the NAT2 slow acetylator phenotype was positively selected for in the transition from hunter-gatherer or nomadic lifestyle to an agricultural or pastoral lifestyle.(3) The prevalence of slow acetylator phenotypes increases with decreasing distance to the equator. Near the equator, up to 80% of individuals may be slow

acetylators, while in some more northern countries, as few as 10% of the population may have the slow acetylator phenotype.

A number of drugs are metabolized by NAT2 including procainamide, dapsone, nitrazepam, hydralazine, sulfasalazine, amifampridine, and isoniazid.(4) Isoniazid is used to treat and prevent tuberculosis and is still used as a primary treatment agent. Adverse reactions with isoniazid, which include nausea, drug-induced hepatitis, peripheral neuropathy, and sideroblastic anemia, are associated more often with a slow NAT2 acetylator phenotype. These individuals may require a lower dose to avoid adverse reactions.(4) Of note, acetaminophen is a significant NAT2 inhibitor.

The *NAT2* gene contains a single intronless exon of 870 base pairs and encodes 290 amino acids. *NAT2* is highly polymorphic and contains at least 16 known single nucleotide variants and 1 single base pair deletion. These genetic variants are combined into 36 known haplotypes or alleles. Each individual haplotype is predictive of either a rapid (fast) or slow acetylator phenotype. Individuals with 2 rapid haplotypes are predicted to be rapid (normal) metabolizers, while those with 1 rapid and 1 slow haplotype are intermediate metabolizers, and those with 2 slow haplotypes are poor metabolizers.(5,6) Studies with patients who have different acetylator haplotypes have correlated the ratio of plasma N-acetylisoniazid/isoniazid drug concentrations with haplotypes, with slow and intermediate acetylators having lower ratios than rapid acetylators.(7)

NAT2 genotype results are used to predict metabolizer phenotypes, as indicated in the Table. Note that the reference allele for *NAT2* is *4. If no variants are detected, the default genotype and phenotype reported are *4/*4 and rapid acetylator phenotype, respectively.

Table.

***NAT2* allele**	**Predicted acetylator phenotype**
**4*	Rapid (normal)
**5*	Slow
**6*	Slow
**7*	Slow
**10*	Slow, but may be substrate dependent
**12D*	Slow
**14*	Slow
**17*	Slow
**19*	Slow

Reference Values

An interpretive report will be provided.

Interpretation

An interpretive report will be provided. The wild-type (normal) genotype for *NAT2* is *4. This is the most commonly occurring allele in some, but not all, ethnic groups.(8)

Individuals are classified as being slow, intermediate, or rapid (fast) acetylators depending on their diplotypes. Slow acetylators have 2 slow haplotypes, rapid acetylators have 2 rapid (fast, normal) haplotypes, and intermediate

acetylators have one of each.

The genotype, with associated star alleles, is assigned using standard allelic nomenclature as described by the Human *NAT2* Alleles (Haplotypes) Database (http://nat.mbg.duth.gr/Human%20NAT2%20alleles_2013.htm).

For additional information regarding pharmacogenomic genes and their associated drugs, see Pharmacogenomic Associations Tables. This resource also includes information regarding enzyme inhibitors and inducers, as well as potential alternate drug choices.

Drug-drug interactions and drug-metabolite inhibition must be considered when adjusting medication dosage. It is important to interpret the results of testing and dose adjustments in the context of hepatic and renal function and patient age. For applicable medications, therapeutic drug monitoring is useful to verify that the drug concentration is within the therapeutic range.

Cautions

Rare variants (ie, polymorphisms) may be present that could lead to false-negative or false-positive results. If results obtained do not match the clinical findings (phenotype), additional testing should be considered.

Samples may contain donor DNA if obtained from patients who received nonleukoreduced blood transfusions or allogeneic hematopoietic stem cell transplantation. Results from samples obtained under these circumstances may not accurately reflect the recipient's genotype. For individuals who have received blood transfusions, the genotype usually reverts to that of the recipient within 6 weeks. For individuals who have received allogeneic hematopoietic stem cell transplantation, a pretransplant DNA specimen is recommended for testing.

NAT2 genetic test results in patients who have undergone liver transplantation may not accurately reflect the patient's arylamine *N*-acetyltransferase type 2 (NAT2) status.

This method may not detect all variants that result in altered NAT2 activity. Therefore, absence of a detectable variant does not rule out the possibility that a patient has altered NAT2 metabolism due to other *NAT2* variants that cannot be detected with this method. Furthermore, when 2 or more variants are identified, the cis-/trans-status (whether the variants are on the same or opposite chromosomes) is often not known; therefore, multiple haplotypes may be provided.

Clinical Reference

1. Salazar-Gonzalez RA, Doll MA, Hein DW: Human arylamine N-acetyltransferase 2 genotype-dependent protein expression in cryopreserved human hepatocytes. Sci Rep. 2020 May 5;10(1):7566
2. Meyer UA: Polymorphism of human acetyltransferases. Environ Health Perspect. 1994 Oct;102 Suppl 6(Suppl 6):213-216
3. McDonagh EM, Boukouvala S, Aklillu E, Hein DW, Altman RB, Klein TE: PharmGKB summary: very important pharmacogene information for N-acetyltransferase 2. Pharmacogenetics and Genomics. 2014 Aug;24(8):409-425
4. Hein DW, Millner LM: Arylamine N-acetyltransferase acetylation polymorphisms: paradigm for pharmacogenomic-guided therapy- a focused review. Expert Opin Drug Metab Toxicol. 2021 Jan;17(1):9-21
5. Sabbagh A, Darlu P: Inferring haplotypes at the *NAT2* locus: the computational approach. BMC Genet. 2005 Jun 2;6:30
6. Leff MA, Fretland AJ, Doll MA, Hein DW: Novel human N-acetyltransferase 2 alleles that differ in mechanism for slow acetylator phenotype. J Biol Chem. 1999 Dec 3;274(49):34519-34522
7. Chen B, Li JH, Xu YM, Wang J, Cao XM: The influence of NAT2 genotypes on the plasma concentration of isoniazid and

acetylisoniazid in Chinese pulmonary tuberculosis patients. Clin Chim Acta. 2006 Mar;365(1):104-108
8. Lin HJ, Han CY, Lin BK, Hardy S: Ethnic distribution of slow acetylator mutations in the polymorphic N-acetyltransferase (*NAT2*) gene. Pharmacogenetics. 1994 Jun;4(3):125-134

Performance

Method Description
Genomic DNA is extracted from whole blood or saliva. Genotyping for *NAT2* alleles is performed using a polymerase chain reaction (PCR)-based 5'-nuclease assay. Fluorescently labeled detection probes anneal to the target DNA. PCR is used to amplify the section of DNA that contains the variant. If the detection probe is an exact match to the target DNA, the 5'-nuclease polymerase degrades the probe, the reporter dye is released from the effects of the quencher dye, and a fluorescent signal is detected. Genotypes are assigned based on the allele-specific fluorescent signals that are detected.(Unpublished Mayo method)

PDF Report
No

Day(s) Performed
Monday through Friday

Report Available
3 to 8 days

Specimen Retention Time
Whole blood/Saliva swab: 2 weeks Extracted DNA: 2 months

Performing Laboratory Location
Rochester

Fees & Codes

Fees
- Authorized users can sign in to Test Prices for detailed fee information.
- Clients without access to Test Prices can contact Customer Service 24 hours a day, seven days a week.
- Prospective clients should contact their account representative. For assistance, contact Customer Service.

Test Classification
This test was developed and its performance characteristics determined by Mayo Clinic in a manner consistent with CLIA requirements. It has not been cleared or approved by the US Food and Drug Administration.

CPT Code Information
81479-Unlisted molecular pathology procedure

Test Definition: NAT2Q

N-Acetyltransferase 2 (NAT2) Genotype, Varies

LOINC® Information

Test ID	Test Order Name	Order LOINC® Value
NAT2Q	NAT2 Genotype, V	101141-0

Result ID	Test Result Name	Result LOINC® Value
616425	NAT2 Genotype	101142-8
616426	NAT2 Phenotype	101143-6
616427	Interpretation	69047-9
616428	Additional Information	48767-8
616430	Method	85069-3
616429	Disclaimer	62364-5
616431	Reviewed By	18771-6