Test Definition: CARBR

Carbamazepine Hypersensitivity
Pharmacogenomics, Varies

Overview

Useful For

Identifying individuals with increased risk of carbamazepine- or oxcarbazepine-associated cutaneous adverse reactions

Genetics Test Information

Detection of the *HLA-B*15:02* allele (HLA00165) in the *HLA-B* gene (NM_005514).

Detection of the *HLA-A*31:01* allele (HLA00097) in the *HLA-A* gene (NM_001242758).

Special Instructions

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

Method Name

Qualitative Allele-Specific Real-Time Polymerase Chain Reaction (PCR)

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.

Patient Preparation: A previous hematopoietic stem cell transplant from an allogenic donor will interfere with testing. For information about testing patients who have received a hematopoietic stem cell transplant, call 800-533-1710.

Specimen Type: Whole blood
Container/Tube: Lavender top (EDTA) or yellow top (ACD)
Specimen Volume: 3 mL
Collection Instructions:
1. Invert several times to mix blood.
2. Send whole blood specimen in original tube. **Do not aliquot**.

3. Whole blood collected postnatal from an umbilical cord is also acceptable. See Additional Information.
Specimen Stability Information: Ambient (preferred) 4 days/Refrigerated 4 days/Frozen 4 days
Additional Information:
1. Specimens are preferred to be received within 4 days of collection. Extraction will be attempted for specimens received after 4 days, and DNA yield will be evaluated to determine if testing may proceed.
2. To ensure minimum volume and concentration of DNA are met, the requested volume must be submitted. Testing may be canceled if DNA requirements are inadequate.
3. For postnatal umbilical cord whole blood specimens, maternal cell contamination studies are recommended to ensure test results reflect that of the patient tested. A maternal blood specimen is required to complete maternal cell contamination studies. Order MATCC / Maternal Cell Contamination, Molecular Analysis, Varies on both the cord blood and maternal blood specimens under separate order numbers.

Specimen Type: Saliva
Patient Preparation: Patient should not eat, drink, smoke, or chew gum 30 minutes prior to collection.
Supplies:
DNA Saliva Kit High Yield (T1007)
Saliva Swab Collection Kit (T786)
Container/Tube:
Preferred: High-yield DNA saliva kit
Acceptable: Saliva swab
Specimen Volume: 1 Tube if using T1007 or 2 swabs if using T786
Collection Instructions: Collect and send specimen per kit instructions.
Specimen Stability Information: Ambient (preferred) 30 days/Refrigerated 30 days
Additional Information: Saliva specimens are acceptable but not recommended. Due to lower quantity/quality of DNA yielded from saliva, some aspects of the test may not perform as well as DNA extracted from a whole blood sample. When applicable, specific gene regions that were unable to be interrogated will be noted in the report. Alternatively, additional specimen may be required to complete testing.

Specimen Type: Extracted DNA
Container/Tube:
Preferred: Screw Cap Micro Tube, 2 mL with skirted conical base
Acceptable: Matrix tube, 1 mL
Collection Instructions:
1. The preferred volume is at least 100 mcL at a concentration of 75 ng/mcL.
2. Include concentration and volume on tube.
Specimen Stability Information: Frozen (preferred) 1 year/Ambient/Refrigerated
Additional Information: DNA must be extracted in a CLIA-certified laboratory or equivalent and must be extracted from a specimen type listed as acceptable for this test (including applicable anticoagulants). Our laboratory has experience with Chemagic, Puregene, Autopure, MagnaPure, and EZ1 extraction platforms and cannot guarantee that all extraction methods are compatible with this test. If testing fails, one repeat will be attempted, and if unsuccessful, the test will be reported as failed and a charge will be applied. If applicable, specific gene regions that were unable to be interrogated due to DNA quality will be noted in the report.

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 forms with the specimen:
-Therapeutics Test Request (T831)
-Neurology Specialty Testing Client Test Request (T732)

Specimen Minimum Volume
See Specimen Required

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
Carbamazepine and oxcarbazepine are aromatic anticonvulsants, as are eslicarbazepine, lamotrigine, phenytoin, fosphenytoin, and phenobarbital. Carbamazepine is US Food and Drug Administration (FDA)-approved for the treatment of epilepsy, trigeminal neuralgia, and bipolar disorder. Oxcarbazepine is FDA-approved for the treatment of partial seizures. A minority of carbamazepine- or oxcarbazepine-treated persons have cutaneous adverse reactions that vary in prevalence and severity, with some forms associated with substantial morbidity and mortality. The most severe reactions, such as the Stevens-Johnson syndrome (SJS) and toxic epidermal necrolysis (TEN), are characterized by a blistering rash affecting a variable percentage of the body-surface area. TEN is the rarest of these phenotypes and is associated with mortality of up to 30%. Drug reaction with eosinophilia and systemic symptoms (DRESS) and maculopapular exanthema (MPE) may also be related to carbamazepine exposure. According to the FDA-approved label for carbamazepine, the estimated incidence of SJS-TEN is 1 to 6 cases in 10,000 persons of European ancestry who are exposed to the drug. The rate of SJS-TEN as a result of carbamazepine exposure is about 10 times higher in some Asian countries. According to the FDA label for oxcarbazepine, the rate of TEN and SJS among individuals exposed to oxcarbazepine exceeds the background incidence by a factor of 3- to 10-fold, but this is expected to be an underestimate due to underreporting. The risk for a severe cutaneous adverse reaction is highest within the first few months of initiating therapy, but may not be absent, particularly if therapy is interrupted or reinitiated.

Clinical studies have demonstrated associations between some human leukocyte antigen (HLA) genotypes and drug-associated cutaneous adverse reactions. The presence of the *HLA-B*15:02* allele varies throughout Asia: 10% to 15% frequency in Chinese; 2% to 4% frequency in Southeast Asians and Indians; and less than 1% frequency in Japanese and Koreans. This allele may be found in other populations, but is rare. This allele is strongly associated with greater risk of SJS and TEN in patients treated with carbamazepine or oxcarbazepine and has also been associated with SJS/TEN with

phenytoin use. There is limited evidence associating SJS/TEN/DRESS or MPE and other aromatic anticonvulsants, such as lamotrigine, in patients who are positive for *HLA-B*15:02*, but the FDA has not issued a formal warning.

The *HLA-A*31:01* allele, which has a prevalence of 2% to 5% in Northern European populations, 6% among Hispanic/South American populations, and 8% among Japanese populations, has been significantly associated with greater risk of MPE, DRESS, and SJS/TEN among patients treated with carbamazepine. In the absence of *HLA-A*31:01*, the risk for drug-associated cutaneous adverse reactions is 3.8%, but in the presence of this allele, the risk increases to 26%. The evidence linking other aromatic anticonvulsants with SJS/TEN in the presence of the *HLA-A*31:01* allele is weaker; however, an alternative medication should be chosen with caution.

The FDA-approved label for carbamazepine states that the screening of patients in genetically at-risk populations (ie, patients of Asian descent) for the presence of the *HLA-B*15:02* allele should be carried out prior to initiating treatment with carbamazepine. The FDA-approved label also notes the association of *HLA-A*31:01* allele with drug-associated cutaneous adverse reactions regardless of ancestry, but it does not specifically mandate screening of patients. The FDA-approved label for oxcarbazepine indicates that testing for the presence of the *HLA-B*15:02* allele should be considered in patients with ancestry including genetically at-risk populations prior to initiation of therapy.

According to the FDA label, patients who test positive for *HLA-B*15:02* should not be treated with carbamazepine or oxcarbazepine unless the benefit clearly outweighs the risk. Similarly, the most recent Clinical Pharmacogenetic Implementation Consortium (CPIC) guideline, patients who are *HLA-B*15:02* positive should not be prescribed carbamazepine or oxcarbazepine if alternative agents are available; however, caution should be used in selecting an alternative medication as there is weaker evidence that also links other aromatic anticonvulsants with SJS/TEN in patients positive for *HLA-B*15:02.* Furthermore, phenytoin and fosphenytoin are the subject of a separate CPIC guideline with recommendations to avoid phenytoin and fosphenytoin in *HLA-B*15:02* positive individuals, along with additional recommendations based on *CYP2C9* genotype. Patients who are *HLA-A*31:01* positive should not be prescribed carbamazepine if alternative agents are available. Although very limited evidence links SJS/TEN/DRESS/MPE with other aromatic anticonvulsants when used by *HLA-A*31:01*-positive patients, caution is advised when selecting an alternative medication.

Reference Values

An interpretive report will be provided.

Interpretation

The presence of the *HLA-B*15:02* and/or *HLA-A*31:01* allele confers increased risk for hypersensitivity to carbamazepine. The presence of the *HLA-B*15:02* allele also confers increased risk for hypersensitivity to oxcarbazepine and phenytoin.

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

Cautions

Rare reported or unreported *HLA-A* and *HLA-B* alleles may occur and may interfere with this assay, resulting in a false-positive or false-negative call. Examples of alleles that may interfere include other *HLA-A*31* alleles (including *HLA-A *31:01:23*), *HLA-B*15:13*, *HLA-B*15:31*, *HLA-B*15:55*, *HLA-B*15:88*, *HLA-B*15:89*, *HLA-B*18:20*, *HLA-B*15:112*,

*HLA-B*15:121*, *HLA-B*15:144*, and *HLA-B*15:170*. However, most of these alleles are rare and exist only in specific ancestral populations, and it is not known if any of these subtypes are associated with hypersensitivity. For example, *HLA-B*15:13*, while rare, has been observed more in Asian populations than other populations.

Samples may contain donor DNA if obtained from patients who received non-leukoreduced blood transfusions or allogeneic hematopoietic stem cell transplantation (AHSCT). 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. The impact of AHSCT on risk of adverse cutaneous reactions is not defined in the literature.

Clinical Reference

1. Phillips EJ, Sukasem C, Whirl-Carrillo M, et al. Clinical Pharmacogenetics Implementation Consortium guideline for HLA genotype and use of carbamazepine and oxcarbazepine: 2017 Update. Clin Pharmacol Ther. 2018;103(4):574-581
2. McCormack M, Alfirevic A, Bourgeois S, et al. HLA-A*3101 and carbamazepine-induced hypersensitivity reactions in Europeans. N Engl J Med. 2011;364:1134-1143
3. Amstutz U, Shear NH, Rieder MJ, et al. Recommendations for HLA-B*15:02 and HLA-A*31:01 genetic testing to reduce the risk of carbamazepine-induced hypersensitivity reactions. Epilepsia. 2014;55:496-506
4. Karnes JH, Rettie AE, Somogyi AA, et al. Clinical Pharmacogenetics Implementation Consortium (CPIC) Guideline for CYP2C9 and HLA-B Genotypes and Phenytoin Dosing: 2020 Update. Clin Pharmacol Ther. 2021;109(2):302-309. doi:10.1002/cpt.2008

Performance

Method Description

Genomic DNA is extracted from whole blood. Amplification for the *HLA-B*15:02* and *HLA-A*31:01* alleles and an internal control gene is performed by real-time polymerase chain reaction (PCR) in the presence of SYBR Green, which fluoresces when bound to double-stranded DNA. A genotype is assigned based on the allele-specific SYBR Green fluorescent signals that are detected.(Unpublished Mayo method)

PDF Report

No

Day(s) Performed

Monday through Friday

Report Available

1 to 5 days

Specimen Retention Time

Whole Blood/Saliva: 30 days; Extracted DNA: 3 months

Performing Laboratory Location

Mayo Clinic Laboratories - Rochester Main Campus

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

81381 x 2

LOINC® Information

Test ID	Test Order Name	Order LOINC® Value
CARBR	Carbamazepine PGx Panel, V	94855-4

Result ID	Test Result Name	Result LOINC® Value
610657	HLA-A*31:01 Genotype	79712-6
610658	HLA-B*15:02 Genotype	57979-7
610659	Carbamazepine PGx Panel Phenotype	93308-5
610660	Interpretation	69047-9
610661	Additional Information	48767-8
610662	Method	85069-3
610663	Disclaimer	62364-5
610664	Reviewed by	18771-6