Test Definition: UBA1Q

UBA1 Mutation Quantitative Detection, VEXAS syndrome, Droplet Digital PCR, Varies

Overview

Useful For

Identification of pathogenic variant(s) in the *UBA1* gene in patients presenting with symptoms concerning for or consistent with VEXAS (vacuoles, E1-enzyme, X-linked, autoinflammatory, somatic) syndrome

Genetics Test Information

A highly sensitive quantitative assay for the detection of 7 UBA1 mutations (c.122T>C, p.Met41Thr; c.121A>G, p.Met41Val; c.121A>C, p.Met41Leu; c.118-1G>C, p.?; c.118-2A>C, p.?; c.118-9_118-2del, p.?; and c.167C>T, p.Ser56Phe).

Special Instructions

- Hematopathology Patient Information

Highlights

This test sensitively and specifically detects seven of the most common recurrent somatic mutations in the *UBA1* gene. *UBA1* mutations are responsible for VEXAS (vacuoles, E1-enzyme, X-linked, autoinflammatory, somatic) syndrome, which is a variably aggressive inflammatory condition. VEXAS syndrome patients also often present with blood count and bone marrow abnormalities that can be associated with the presence of myelodysplastic syndrome or other hematologic neoplasms. Detection of *UBA1* mutation is critical for diagnosing VEXAS syndrome. This droplet digital polymerase chain reaction assay offers improved analytical sensitivity over other commonly used test methodologies.

Method Name

Droplet Digital Polymerase Chain Reaction (ddPCR)

NY State Available

Yes

Specimen

Specimen Type

Varies

Ordering Guidance

This test is intended for patients with clinical symptoms and other pertinent laboratory findings raising concern for VEXAS (vacuoles, E1-enzyme, X-linked, autoinflammatory, somatic) syndrome. These may include, but are not limited to, systemic or localized (eg, ear, orbital, skin) tissue inflammation presenting as rheumatologic disease, abnormal (usually low) whole blood counts, macrocytic anemia, characteristic microscopic changes in the bone marrow, as well as others.

Shipping Instructions

1. Both refrigerated and ambient specimens **must arrive within 7 days of collection**.

2. Collect and package specimen as close to shipping time as possible.

Necessary Information

The following information is required:

1. Pertinent clinical history
2. Date of collection
3. Specimen source (blood or bone marrow)

Specimen Required

Submit only 1 of the following specimens:

Specimen Type: Whole blood
Container/Tube:
Preferred: Lavender top (EDTA)
Acceptable: Yellow top (ACD-B) or green top (heparin)
Specimen Volume: 4 mL
Collection Instructions:
1. Invert several times to mix blood.
2. Send whole blood specimen in original tube. **Do not aliquot.**
3. Label specimen as blood.
Specimen Stability: Refrigerated (preferred) 7 days/Ambient 7 days

Specimen Type: Bone marrow aspirate
Container/Tube:
Preferred: Lavender top (EDTA)
Acceptable: Yellow top (ACD-B) or green top (heparin)
Specimen Volume: 2 mL
Collection Instructions:
1. Invert several times to mix bone marrow.
2. Send bone marrow specimen in original tube. **Do not aliquot**.
3. Label specimen as bone marrow.
Specimen Stability: Refrigerated (preferred) 7 days/Ambient 7 days

Specimen Type: Extracted DNA from whole blood or bone marrow
Container/Tube: 1.5- to 2-mL tube
Specimen Volume: Entire specimen
Collection Instructions:
1. DNA must be extracted from blood or bone marrow within 7 days of collection.
2. Label specimen as extracted DNA and source of specimen.
2. Provide volume and concentration of DNA. The minimum required volume 50 mcL at a concentration of 50 ng/mcL
Specimen Stability: Frozen (preferred) 1 year/Refrigerate
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). We 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.

Forms

1. Hematopathology Patient Information (T676)
2. If not ordering electronically, complete, print, and send a Hematopathology/Cytogenetics Test Request (T726) with the specimen.

Specimen Minimum Volume

Whole blood: 4 mL; Bone marrow: 2 mL; Extracted DNA: 50 mcL at 50 ng/mcL

Reject Due To

Gross hemolysis	Reject
Moderately to severely clotted	Reject

Specimen Stability Information

Specimen Type	Temperature	Time	Special Container
Varies	Refrigerated (preferred)	7 days	
	Ambient	7 days	

Clinical & Interpretive

Clinical Information

VEXAS (vacuoles, E1-enzyme, X-linked, autoinflammatory, somatic) syndrome is caused by somatic mutations in the *UBA1* gene, which is located on the X-chromosome and encodes ubiquitin-activating enzyme E1, an important component in the protein ubiquitylation process. This syndrome, identified in 2020, is characterized by adult-onset rheumatologic and hematologic manifestations. Inflammatory disease can present systemically, as well with more localized findings involving the orbit, skin or ears. Hematologic abnormalities are frequently present, including low blood counts, macrocytic anemia, and characteristic vacuolated myeloid and erythroid precursor cells in the bone marrow.(1) VEXAS syndrome occurs overwhelmingly in male patients, suggesting that biologic females who might acquire a *UBA1* mutation may be relatively protected by the presence of the remaining normal wild type allele.(2) To date, nearly all documented cases of VEXAS syndrome have been caused by seven mutations that occur at three different sites within exon 3 of the *UBA1* gene: the intron 2 acceptor splice site and p.Met41 codon region (c.118-122), and the p.Ser56 codon (c.167).(1-4) Importantly, a significant number of VEXAS patients may have predisposition to develop bone marrow failure, clonal hematopoiesis, myelodysplastic syndrome, or other hematologic neoplasms (eg, plasma cell neoplasms).(2-4) Patients with *UBA1* mutation and features of bone marrow failure appear to be associated with poor prognosis and may not respond to standard immunosuppressive and hypomethylating agents typically utilized in the treatment of autoinflammatory disorders and myelodysplastic syndrome.(3,4) Testing for these mutations will serve to identify VEXAS syndrome patients who should be considered for alternative therapies or clinical trials.

Reference Values

An interpretive report will be provided.

Interpretation

The assay is reported as positive or negative. In positive cases, the mutation type and its variant allele fraction (VAF) are reported.

VAF%= (mutant copy number)/(mutant copy number + wild-type number)

The precision of this quantitative assay is very high but inter-assay variability may occur such that quantitative changes should not be considered significant if 2 single measurements differ by less than 0.5 log (3.16-fold).

Cautions

Other potential *UBA1* variants outside the 7 assay targets are not detected by this assay. The absence of *UBA1* mutation does not exclude other causes of inflammatory disorders or clonal myeloid processes. Although most patients with VEXAS (vacuoles, E1-enzyme, X-linked, autoinflammatory, somatic) syndrome have high *UBA1* mutation variant fractions, this assay may not identify very low mutation burden cases below the limit of detection.

Clinical Reference

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2. Grayson PC, Patel BA, Young NS. VEXAS syndrome. Blood. 2021;137(26):3591-3594
3. Huang H, Zhang W, Cai W, et al. VEXAS syndrome in myelodysplastic syndrome with autoimmune disorder. Exp Hematol Oncol. 2021;10(1):23
4. Gutierrez-Rodrigues F, Kusne Y, Fernandez J, et al. Spectrum of clonal hematopoiesis in VEXAS syndrome. Blood. 2023;142(3):244-259
5. Koster MJ, Warrington KJ. VEXAS within the spectrum of rheumatologic disease. Semin Hematol. 2021;58(4):218-225
6. Obiorah IE, Patel BA, Groarke EM, et al. Benign and malignant hematologic manifestations in patients with VEXAS syndrome due to somatic mutations in UBA1. Blood Adv. 2021;5(16):3203-3215
7. Oganesyan A, Hakobyan Y, Terrier B, Georgin-Lavialle S, Mekinian A. Looking beyond VEXAS: Coexistence of undifferentiated systemic autoinflammatory disease and myelodysplastic syndrome. Semin Hematol. 2021;58(4):247-253
8. Poulter JA, Savic S. Genetics of somatic auto-inflammatory disorders. Semin Hematol. 2021;58(4):212-217
9. Shaukat F, Hart M, Burns T, Bansal P. UBA1 and DNMT3A mutations in VEXAS syndrome. A case report and literature review. Mod Rheumatol Case Rep. 2022;6(1):134-139. doi:10.1093/mrcr/rxab021
10. Zakine E, Schell B, Battistella M, et al. UBA1 variations in neutrophilic dermatosis skin lesions of patients with VEXAS syndrome. JAMA Dermatol. 2021;157(11):1349-1354
11. Corty RW, Brogan J, Byram K, Springer J, Grayson PC, Bick AG. VEXAS-Defining UBA1 Somatic Variants in 245,368 Diverse Individuals in the NIH All Of Us Cohort. Arthritis Rheumatol. 2024;76(6):942-948. doi:10.1002/art.42802
12. Echerbault R, Bourguiba R, Georgin-Lavialle S, Lavigne C, Ravaiau C, Lacombe V. Comparing clinical features between males and females with VEXAS syndrome: data from literature analysis of patient reports. Rheumatology. 2024;63(10):2694-2700

Performance

Method Description
This test is performed using a droplet digital polymerase chain reaction (ddPCR) system. DNA extracted from patient samples is PCR-amplified using oligonucleotide primers and mutant- and wildtype-specific fluorescently labeled probes directed to the genomic target regions. Results are analyzed using dedicated software and Poisson statistics to provide absolute quantification of mutant target and wild type copies. Calculated results are reported as mutant fractional abundance (variant allele fraction %).(Unpublished Mayo method)

PDF Report
No

Day(s) Performed
Monday through Saturday

Report Available
4 to 8 days

Specimen Retention Time
Whole blood/bone marrow: 2 weeks; 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
81403

LOINC® Information

Test ID	Test Order Name	Order LOINC® Value
UBA1Q	UBA1 Mutation, Quant, ddPCR, V	104268-8

Test Definition: UBA1Q

UBA1 Mutation Quantitative Detection, VEXAS syndrome, Droplet Digital PCR, Varies

Result ID	Test Result Name	Result LOINC® Value
MP086	Specimen Type	31208-2
620938	Interpretation	59465-5
620939	Signing Pathologist	19139-5