MAYO CLINIC LABORATORIES

Test Definition: GATAS

GATA-Binding Protein 2, GATA2, Full Gene Analysis, Next-Generation Sequencing, Varies

Overview

Useful For

Comprehensive evaluation of the *GATA2* gene in patients with clinical or immunological symptoms suggestive of GATA-binding protein 2 (GATA2) deficiency

Screening family members of patients with confirmed GATA2 deficiency

Reflex Tests

Test Id	Reporting Name	Available Separately	Always Performed
CULFB	Fibroblast Culture for Genetic Test	Yes	No

Genetics Test Information

This test utilizes next-generation sequencing to detect single nucleotide and copy number variants in the *GATA2* gene associated with GATA-binding protein 2 (GATA2) deficiency.

Identification of a disease-causing variant may assist with diagnosis, prognosis, clinical management, recurrence risk assessment, familial screening, and genetic counseling for GATA2 deficiency.

Testing Algorithm

For skin biopsy or cultured fibroblast specimens, fibroblast culture will be performed at an additional charge. If viable cells are not obtained, the client will be notified.

Special Instructions

- Informed Consent for Genetic Testing
- GATA2 Gene Sequencing Patient Information
- Informed Consent for Genetic Testing (Spanish)

Method Name

Sequence Capture and Targeted Next-Generation Sequencing (NGS) followed by Polymerase Chain Reaction (PCR) and Sanger Sequencing

NY State Available

Yes

Specimen

Specimen Type

Varies

Ordering Guidance

For cases where the differential diagnosis remains broad, *GATA2* may be evaluated as part of a gene panel. See HLHGP / Primary Hemophagocytic Lymphohistiocytosis (HLH) Gene Panel, Varies; SCCNP / Severe Congenital and Cyclic Neutropenia Gene Panel, Varies; or EBLPD / Epstein Barr Virus (EBV) Susceptibility and Lymphoproliferative Disorders Gene Panel, Varies.

Targeted testing for familial variants (also called site-specific or known variants testing) is available for variants identified in the GATA2 gene. See FMTT / Familial Variant, Targeted Testing, Varies. To obtain more information about testing option, call 800-533-1710.

Shipping Instructions

Specimen preferred to arrive within 96 hours of collection.

Specimen Required

Patient Preparation: A previous bone marrow transplant from an allogenic donor will interfere with testing. Call 800-533-1710 for instructions for testing patients who have received a bone marrow transplant.

Submit only 1 of the following specimens:

Specimen Type: Whole blood
Container/Tube:
Preferred: Lavender top (EDTA) or yellow top (ACD)
Acceptable: Any anticoagulant
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) 4 days/Refrigerated

Specimen Type: Skin biopsy
Supplies: Fibroblast Biopsy Transport Media (T115)
Container/Tube: Sterile container with any standard cell culture media (eg, minimal essential media, RPMI 1640). The solution should be supplemented with 1% penicillin and streptomycin.
Specimen Volume: 4-mm punch
Specimen Stability Information: Refrigerated (preferred)/Ambient
Additional Information: A separate culture charge will be assessed under CULFB / Fibroblast Culture for Biochemical or Molecular Testing. An additional 3 to 4 weeks is required to culture fibroblasts before genetic testing can occur.

Specimen Type: Cultured fibroblasts
Container/Tube: T-25 flask
Specimen Volume: 2 Flasks
Collection Instructions: Submit confluent cultured fibroblast cells from a skin biopsy from another laboratory. Cultured

cells from a prenatal specimen will not be accepted.
Specimen Stability Information: Ambient (preferred)/Refrigerated (<24 hours)
Additional Information: A separate culture charge will be assessed under CULFB / Fibroblast Culture for Biochemical or Molecular Testing. An additional 3 to 4 weeks is required to culture fibroblasts before genetic testing can occur.

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. GATA2 Gene Sequencing Patient Information (T811) is recommended.

Specimen Minimum Volume

Blood: 1 mL; Skin biopsy or cultured fibroblasts: 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

GATA-binding protein 2 (GATA2) deficiency causes multiple previously distinct clinical entities, including DCML deficiency (dendritic cell, monocyte, B and natural killer [NK] cell lymphocyte deficiency), MonoMAC syndrome (monocytopenia with *Mycobacterium avium* complex infection), Emberger syndrome (myelodysplastic syndrome [MDS] with lymphedema), NK cell deficiency, and familial MDS/acute myeloid leukemia. As such, there is a wide spectrum of clinical features, including severe viral infections (particularly with human papillomavirus, molluscum contagiosum, herpes simplex virus, Epstein-Barr virus, and cytomegalovirus), warts, fungal infections (particularly histoplasmosis and aspergillosis), mycobacterial infections, pulmonary alveolar proteinosis, bone marrow hypocellularity, neutropenia, sensorineural hearing loss, and congenital lymphedema. Immunological phenotypes include dendritic cell, monocyte, CD4+ T cell, B- and NK- cell deficiencies. Also, the loss of a specific NK-cell subset, CD56 bright NK cells, has been reported in these patients.

GATA2 is a zinc finger transcription factor involved in hematopoiesis, maintenance of the hematopoietic stem cell (HSC) pool, and for HSC progenitor differentiation. Disease-causing genetic variants in *GATA2* result in loss-of-function and haploinsufficiency and are transmitted in an autosomal dominant manner or arise *de novo*. Null variants (frameshift, nonsense, splicing, and large deletions) account for most cases, while missense variants account for approximately 30% of cases, and noncoding variants in an intronic enhancer element and synonymous variants that impact splicing account for the remainder of cases. Genotype-phenotype correlations are difficult to make, as there is considerable clinical heterogeneity. Incomplete penetrance has been observed with GATA2 deficiency, and the age at

presentation varies; however, by age 60 years, the penetrance is estimated to be 90%. Additionally, there may be a role for environmental factors triggering certain infectious manifestations.

The definitive treatment for GATA2 deficiency is HSC transplantation. Early genetic diagnosis of GATA2 deficiency may aid in selecting management strategies and allow for family screening and counseling.

Reference Values

An interpretive report will be provided

Interpretation

All detected variants are evaluated according to American College of Medical Genetics and Genomics (ACMG) recommendations.(1) Variants are classified based on known, predicted, or possible pathogenicity and reported with interpretive comments detailing their potential or known significance.

Cautions

Clinical Correlations:
Test results should be interpreted in the context of clinical findings, family history, and other laboratory data. Misinterpretation of results may occur if the information provided is inaccurate or incomplete.

If testing was performed because of a clinically significant family history, it is often useful to first test an affected family member. Detection of a reportable variant in an affected family member would allow for more informative testing of at-risk individuals.

To discuss the availability of additional testing options or for assistance in the interpretation of these results, contact Mayo Clinic Laboratories genetic counselors at 800-533-1710.

Technical Limitations:
Next-generation sequencing may not detect all types of genomic variants. In rare cases, false-negative or false-positive results may occur. The depth of coverage may be variable for some target regions; assay performance below the minimum acceptable criteria or for failed regions will be noted. Given these limitations, negative results do not rule out the diagnosis of a genetic disorder. If a specific clinical disorder is suspected, evaluation by alternative methods can be considered.

There may be regions of genes that cannot be effectively evaluated by sequencing or deletion and duplication analysis as a result of technical limitations of the assay, including regions of homology, high guanine-cytosine (GC) content, and repetitive sequences. Confirmation of select reportable variants will be performed by alternate methodologies based on internal laboratory criteria.

This test is validated to detect 95% of deletions up to 75 base pairs (bp) and insertions up to 47 bp. Deletions-insertions (delins) of 40 or more bp, including mobile element insertions, may be less reliably detected than smaller delins.

Deletion/Duplication Analysis:
This analysis targets single and multi-exon deletions/duplications; however, in some instances, single exon resolution cannot be achieved due to isolated reduction in sequence coverage or inherent genomic complexity. Balanced structural rearrangements (such as translocations and inversions) may not be detected.

Deletion/duplication events that extend past the genes included on the panel may occur. In these instances, genes included in the ordered test are provided on the report and interpreted, and genomic breakpoints are reported if they are confirmed. However, copy number variants for genes not listed in the Method Description are typically not reported or interpreted for haploinsufficiency/triplosensitivity. CMACB / Chromosomal Microarray, Congenital, Blood; WESPR / Panel to Whole Exome Sequencing Reflex Test, Varies; or WGSDX / Whole Genome Sequencing for Hereditary Disorders, Varies is recommended for a full interpretation of deletions/duplications predicted to extend past the genes included on the panel.

This test is not designed to detect low levels of mosaicism or to differentiate between somatic and germline variants. If there is a possibility that any detected variant is somatic, additional testing may be necessary to clarify the significance of results.

For detailed information regarding gene specific performance and technical limitations, see Method Description or contact a laboratory genetic counselor.

If the patient has had an allogeneic hematopoietic stem cell transplant or a recent non-leukoreduced blood transfusion, results may be inaccurate due to the presence of donor DNA. Call Mayo Clinic Laboratories for instructions for testing patients who have received a bone marrow transplant.

Reclassification of Variants**:**
Currently, it is not standard practice for the laboratory to systematically review previously classified variants on a regular basis. The laboratory encourages health care providers to contact the laboratory at any time to learn how the classification of a particular variant may have changed over time. Due to broadening genetic knowledge, it is possible that the laboratory may discover new information of relevance to the patient. Should that occur, the laboratory may issue an amended report.

Variant Evaluation:
Evaluation and categorization of variants are performed using published American College of Medical Genetics and Genomics and the Association for Molecular Pathology recommendations as a guideline.(1) Other gene-specific guidelines may also be considered. Variants are classified based on known, predicted, or possible pathogenicity and reported with interpretive comments detailing their potential or known significance. Variants classified as benign or likely benign are not reported.

Multiple in silico evaluation tools may be used to assist in the interpretation of these results. The accuracy of predictions made by in silico evaluation tools is highly dependent upon the data available for a given gene, and periodic updates to these tools may cause predictions to change over time. Results from in silico evaluation tools should be interpreted with caution and professional clinical judgment.

Rarely, incidental or secondary findings may implicate another predisposition or presence of active disease. These findings will be carefully reviewed to determine whether they will be reported.

Clinical Reference

1. Richards S, Aziz N, Bale S, et al; ACMG Laboratory Quality Assurance Committee: Standards and guidelines for the

interpretation of sequence variants: a joint consensus recommendation of the American College of Medical Genetics and Genomics and the Association for Molecular Pathology. Genet Med. 2015 May;17(5):405-424
2. Fabozzi F, Mastronuzzi A, Ceglie G, Masetti R, Leardini D: GATA 2 deficiency: Focus on immune system impairment. Frong Immunol. 2022 Jun 13;13:865773
3. Hsu AP, McReynolds LJ, Holland SM: GATA2 deficiency. Curr Opin Allergy Clin Immunol. 2015 Feb;15(1):104-109
4. Bresnick EH, Jung MM, Katsumura KR: Human GATA2 mutations and hematologic disease: how many paths to pathogenesis? Blood Adv. 2020 Sep 22;4(18):4584-4592
5. Kozyra EJ, Pastor VB, Lefkopoulos S, et al: Synonymous GATA2 mutations result in selective loss of mutated RNA and are common in patients with GATA2 deficiency. 2020 Oct;34(10):2673-2687
6. Tangye SG, Al-Herz W, Bousfiha A, et al: Human inborn errors of immunity: 2022 update on the classification from the International Union of Immunological Societies Expert Committee. J Clin Immunol. 2022 Oct;42(7):1473-1507. doi: 10.1007/s10875-022-01289-3

Performance

Method Description

Next-generation sequencing (NGS) and/or Sanger sequencing are performed to test for the presence of variants in coding regions and intron/exon boundaries of the *GATA2* gene, as well as some other regions that have known disease-causing variants. The human genome reference GRCh37/hg19 build was used for sequence read alignment. At least 99% of the bases are covered at a read depth over 30X. Sensitivity is estimated at above 99% for single nucleotide variants, above 94% for deletions/insertions (delins) less than 40 base pairs (bp), and above 95% for deletions up to 75 bp and insertions up to 47 bp. NGS and/or a polymerase chain reaction-based quantitative method is performed to test for the presence of deletions and duplications in the *GATA2* gene.

There may be regions of *GATA2* gene that cannot be effectively evaluated by sequencing or deletion and duplication analysis as a result of technical limitations of the assay, including regions of homology, high guanine-cytosine (GC) content, and repetitive sequences.(Unpublished Mayo method)

Confirmation of select reportable variants may be performed by alternate methodologies based on internal laboratory criteria.

Reference transcript numbers may be updated due to transcript re-versioning. Always refer to the final patient report for gene transcript information referenced at the time of testing.

Gene symbol	Reference transcript	Additional evaluations	Technical limitations
GATA2	NM_032638.5	c.1017+526_1017+589 corresponding to a highly conserved intronic region c.1018-17_1020	-

PDF Report

Supplemental

Day(s) Performed
Varies

Report Available
28 to 42 days

Specimen Retention Time
Whole blood: 2 weeks (if available); Extracted DNA: 3 months; Cultured fibroblasts, skin biopsy: 1 month

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
81479
88233- Tissue culture, skin, solid tissue biopsy (if appropriate)
88240- Cryopreservation (if appropriate)

LOINC® Information

Test ID	Test Order Name	Order LOINC® Value
GATAS	GATA2 Gene, Full Gene Analysis	95771-2

Result ID	Test Result Name	Result LOINC® Value
619803	Test Description	62364-5
619804	Specimen	31208-2
619805	Source	31208-2
619806	Result Summary	50397-9
619807	Result	82939-0
619808	Interpretation	69047-9
619809	Additional Results	82939-0
619810	Resources	99622-3

619811	Additional Information	48767-8
619812	Method	85069-3
619813	Genes Analyzed	82939-0
619814	Disclaimer	62364-5
619815	Released By	18771-6