Test Definition: GATA2

GATA2 Comprehensive Gene Sequencing

Overview

Useful For

A 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

Genetics Test Information

This test includes next-generation sequencing and supplemental Sanger sequencing.

Identification of a pathogenic variant may assist with prognosis, clinical management, familial screening, and genetic counseling.

Highlights

This test may aid in the diagnosis of GATA2 deficiency.

Reflex Tests

Test ID	Reporting Name	Available Separately	Always Performed
FIBR	Fibroblast Culture	Yes	No
CRYOB	Cryopreserve for Biochem Studies	No	No

Testing Algorithm

For skin biopsy or cultured fibroblast specimens, fibroblast culture and cryopreservation testing 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

Custom Sequence Capture and Targeted Next-Generation Sequencing

NY State Available

Yes

Specimen

Specimen Type

Varies

Advisory Information

Targeted testing for familial variants (also called site-specific or known mutations testing) is available for this gene.

See FMTT / Familial Mutation, Targeted Testing, Varies.

Necessary Information

1. GATA2 Gene Sequencing Patient Information **is required.** See Special Instructions Testing may proceed without the Patient Information however it aids in providing a more thorough interpretation. Ordering physicians are strongly encouraged to fill out the form.

2. Include physician name and phone number with the specimen.

Specimen Required

Submit only 1 of the following specimens:

Preferred:

Specimen Type: Whole blood

Container/Tube: Lavender top (EDTA)

Specimen Volume: 3 mL

Collection Instructions:

1. Invert several times to mix blood.

2. Send specimen in original tube.

Specimen Stability Information: Ambient (preferred) 4 days/Refrigerated 14 days

Specimen Type: Peripheral blood mononuclear cells (PBMCs)

Container/Tube: Cell pellet

Collection Instructions: Send as a suspension in freezing medium or cell pellet frozen on dry ice.

Specimen Stability Information: Frozen

Specimen Type: Cultured fibroblasts

Container/Tube: T-75 or T-25 flask

Specimen Volume: 1 Full T-75 or 2 full T-25 flasks

Additional Information: Indicate the tests to be performed on the fibroblast culture cells.

Specimen Stability Information: Ambient (preferred)/Refrigerated <24 hours

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. Tubes of culture media can be supplied upon request (Eagle's minimum essential medium with 1% penicillin and streptomycin).

Specimen Volume: 4-mm punch

Additional Information: A separate culture charge will be assessed under FIBR / Fibroblast Culture. An additional 4 weeks is required to culture fibroblasts before genetic testing can occur.

Specimen Stability Information: Refrigerated (preferred)/Ambient

Specimen Type: 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 250 ng/mcL

2. Include concentration and volume on tube.

Specimen Stability Information: Frozen (preferred)/Ambient/Refrigerated

Forms

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 in Special Instructions:

-Informed Consent for Genetic Testing (T576)

-Informed Consent for Genetic Testing-Spanish (T826)

Specimen Minimum Volume

Whole blood: 1 mL

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 and Interpretive

Clinical Information

GATA-binding protein 2 (GATA2) deficiency is emerging as the second most common primary immunodeficiency

disorder (PIDD) or inborn error of immunity in adults, after common variable immunodeficiency (CVID). There is a spectrum of clinical presentations associated with GATA2 deficiency, including severe viral infections (eg, human papillomavirus [HPV]), warts, fungal infections, bacterial infections (eg, atypical mycobacterial infections such as nontuberculous mycobacterial infections [NTM] or mycobacterium avium complex [MAC]), myelodysplastic syndrome (MDS), acute myeloid leukemia (AML), and Emberger syndrome (primary lymphedema with MDS). Other clinical phenotypes of GATA2 deficiency may include aplastic anemia, pulmonary alveolar proteinosis (PAP), sensorineural hearing loss, neutropenia, and congenital lymphedema without MDS at diagnosis. Immunological phenotypes include dendritic cell, monocyte, CD4+ T cell, B and natural killer (NK) cell deficiencies. Also, the loss of a specific NK-cell subset, CD56 bright NK cells, has been reported in these patients. GATA2 deficiency was first described in 2011 as being associated with either MonoMAC (monocytopenia and mycobacterial infection) syndrome or DCML deficiency (dendritic cell, monocyte, B and NK cell lymphocyte deficiency).

GATA2 is a zinc finger transcription factor, involved in the generation and function of hematopoietic stem cell progenitors and, therefore, affects several of the subsequent cell lineages.

GATA2 deficiency is a disease of haploinsufficiency, and most germline variants appear to arise de novo (spontaneously) but are then transmitted in an autosomal dominant manner. Standard genotype-phenotype correlations are difficult to make, as there is considerable clinical heterogeneity and the age of presentation varies from early childhood to late in adult life. Additionally, there may be a role for environmental factors triggering certain infectious manifestations. There has been incomplete penetrance (not every individual with a variant has a clinical phenotype) observed with GATA2 deficiency as well as variable expressivity (different clinical presentations for the same genetic variant).The genetic alterations observed in *GATA2* are heterogeneous, and include missense variants, nonsense variants, and variants in the regulatory region of intron 5, in-frame deletions involving the C-terminal zinc finger domain, frameshift variants, and large deletions. The latter are associated with null alleles, while regulatory variants have been observed in the enhancer region of intron 5.

Somatic variants in *ASXL1* have been reported in GATA2 deficiency patients and have been postulated to be associated with transformation to myeloid leukemia. The definitive treatment for GATA2 deficiency is hematopoietic cell transplantation (HCT). Additionally, systemic use of interferon-alpha may be helpful in patients with NK cell deficiency who have recurrent or severe HPV or herpes virus infections. Also, prophylactic antibiotics may be needed or mandated in the nontransplanted patient. The pulmonary alveolar proteinosis observed in GATA2 deficiency is in the context of negative results for anti-GM-CSF autoantibodies has been shown to improve after HCT and suggests correction of alveolar macrophage function.

Early genetic diagnosis of GATA2 deficiency is critical in determining strategies for managing the disease considering the broad clinical spectrum. Genetic diagnosis by confirmation of a pathogenic *GATA2* variant may also aid in family counseling and screening.

Reference Values

An interpretive report will be provided.

Interpretation

Evaluation and categorization of variants is performed using the most recent published American College of Medical Genetics and Genomics (ACMG) recommendations. Variants are classified based on known, predicted, or possible pathogenicity and reported with interpretive comments detailing their potential or known significance.

Unless reported or predicted to cause disease, alterations found deep in the intron or alterations that do not result in an amino acid substitution are not reported.

Cautions

The nomenclature of variants identified in the *GATA2* gene may vary depending on the reference transcript used. When comparing the result to published literature this fact should be kept in mind.

CLINICAL CORRELATIONS:

Some individuals who have involvement of one or more of the genes on the panel may have a variant that is not identified by the methods performed (eg, promoter variants, deep intronic variants). The absence of a variant, therefore, does not eliminate the possibility of disease. Test results should be interpreted in context of clinical findings, family history, and other laboratory data. Misinterpretation of results may occur if the information provided is inaccurate or incomplete.

For predictive testing of asymptomatic individuals, it is often useful to first test an affected family member. Identification of a pathogenic variant in an affected individual allows for more informative testing of at-risk individuals.

TECHNICAL LIMITATIONS:

Next-generation sequencing may not detect all types of genetic variants. Additionally, rare variants may be present that could lead to false-negative or false-positive results. If results do not match clinical findings, consider alternative methods for analyzing these genes, such as Sanger sequencing or large deletion/duplication analysis.

If the patient has had an allogeneic blood or bone marrow transplant or a recent (ie, <6 weeks from time of sample collection) heterologous blood transfusion, results may be inaccurate due to the presence of donor DNA.

EVALUATION TOOLS:

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 predictions made by these tools may change over time. Results from in silico evaluation tools should be interpreted with caution and professional clinical judgment.

Reclassification of Variants-Policy:

At this time, it is not standard practice for the laboratory to systematically review likely pathogenic variants or variants of uncertain significance that are detected and reported. The laboratory encourages health care providers to contact the laboratory at any time to learn how the status of a particular variant may have changed over time. Consultation with a healthcare provider, or team of healthcare providers, with expertise in genetics and primary immunodeficiencies, is recommended for interpretation of this result.

A list of benign and likely benign variants detected is available from the lab upon request.

Contact the laboratory if additional information is required regarding the transcript or human genome assembly used for the analysis of results.

Clinical Reference

1. Spinner MA, Sanchez LA, Hsu AP, et al: GATA2 deficiency: a protean disorder of hematopoiesis, lymphatics and immunity. Blood 2014;123:809-821

2. Dickinson RE, Griffin H, Bigley V, et al: Exome sequencing identifies GATA-2 mutation as the cause of dendritic cells, monocyte, B and NK lymphoid deficiency. Blood 2011;118:2656-2658

3. Hsu AP, Sampaio EP, Khan J, et al: Mutations in *GATA2* are associated with the autosomal dominant and sporadic monocytopenia and mycobacterial infection (MonoMAC) syndrome. Blood 2011;118:2653-2655

4. Mace EM, Hsu AP, Monaco-Shawver L, et al: Mutations in *GATA2* cause human NK cell deficiency with specific loss of the CD56bright subset. Blood 2013;121:2669-2677

5. Ostergaard P, Simpson MA, Connell FC, et al: Mutations in *GATA2* cause primary lymphedema associated with a predisposition to acute myeloid leukemia (Emberger syndrome). Nature Genetics 2011;43:929-931

6. West RR, Hsu AP, Holland SM, et al: Acquired *ASXL1* mutations are common in patients with inherited GATA2 mutations and correlate with myeloid transformation. Haematologica 2014;99:276-281

7. Cuellar-Rodriguez J, Gea-Banacloche J, Freeman AF, et al: Successful allogeneic hematopoietic stem cell transplantation for GATA2 deficiency. Blood 2011;118:3715-3720

8. Hsu AP, McReynolds LJ, Holland SM: GATA2 deficiency. Curr Opin Allergy Clin Immunol 2015;15:104-109

Performance

Method Description

Next-generation sequencing (NGS) is performed using an Illumina instrument with paired-end reads. The DNA is prepared for NGS using a custom Agilent SureSelect Target Enrichment System. Data is analyzed with a bioinformatics software pipeline.(Unpublished Mayo method)

PDF Report

No

Day(s) and Time(s) Test Performed

Monday; Varies

Analytic Time

2 weeks

Maximum Laboratory Time

4 weeks

Specimen Retention Time

Extracted DNA: 2 months

Performing Laboratory Location

Rochester

Fees and 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 Regional Manager. 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. This test has not been cleared or approved by the U.S. Food and Drug Administration.

CPT Code Information

81479

LOINC® Information

Test ID	Test Order Name	Order LOINC Value
GATA2	GATA2 Comprehensive Gene Sequencing	95771-2

Result ID	Test Result Name	Result LOINC Value
92332	Result Summary	50397-9
92333	Result Details	82939-0
92334	Interpretation	69047-9
92335	Additional Information	48767-8
92336	Method	49549-9
92337	Disclaimer	62364-5
92338	Reviewed by	18771-6