Test Definition: GNMY9

MYH9-Related Disorders, MYH9 Gene,
Next-Generation Sequencing, Varies

Overview

Useful For

Evaluating *MYH9*-related disorders, including May-Hegglin disorder/anomaly and Sebastian syndrome, in patients with a personal or family history suggestive of an *MYH9*-related disorder

Diagnosing *MYH9*-related disorders, including May-Hegglin disorder/anomaly and Sebastian syndrome, for patients in whom phenotypic testing is nondiagnostic, but there is a strong clinical suspicion of the *MYH9*-related disorder

Confirming an *MYH9*-related disorder diagnosis with the identification of a known or suspected disease-causing alteration in the *MYH9* gene

Determining the disease-causing alterations within the *MYH9* gene to delineate the underlying molecular defect in a patient with a laboratory diagnosis of an *MYH9*-related disorder

Identifying the causative alteration for genetic counseling purposes

Prognosis and risk assessment based on the genotype-phenotype correlations

Providing a prognosis in syndromic *MYH9*-related disorders

Carrier testing for close family members of an individual with an *MYH9*-related disorder diagnosis

This test is **not intended for** prenatal diagnosis

Genetics Test Information

This test utilizes next-generation sequencing to detect single nucleotide and copy number variants in the *MYH9* gene associated with *MYH9*-related disorders, including May-Hegglin disorder/anomaly and Sebastian syndrome. See Method Description for additional details.

Identification of a disease-causing alteration may assist with diagnosis, prognosis, clinical management, recurrence risk assessment, familial screening, and genetic counseling for *MYH9*-related disorders, including May-Hegglin disorder/anomaly and Sebastian syndrome.

Testing Algorithm

The clinical workup for detecting inherited platelet disorders should begin with a careful review of a patient's complete blood cell count and platelet indices results, peripheral blood smear, and other platelet tests, such as light transmission platelet aggregometry, electrical impedance whole blood aggregometry, and platelet function analyzer 100 (PFA-100). Platelet transmission electron microscopy is an essential tool for laboratory diagnosis of various hereditary platelet disorders, and platelet flow cytometric analysis is the preferred method to assess hereditary platelet disorders due to quantitative surface glycoprotein deficiencies

Due to the reduced sensitivity of functional testing, occasionally, the clinical picture may be consistent with a defect in primary hemostasis, but results of platelet tests may be normal or non-diagnostic.

Genetic testing for hereditary platelet disorders is indicated if:
-Platelet tests indicate a deficiency or functional abnormality, and abnormal platelet or white blood cell morphology by light or electron microscopy
-There is a clinical suspicion for a hereditary platelet disorder due to family history or patient's clinical presentation
-Acquired causes of deficiencies associated with platelet disorders have been excluded

If a platelet disorder is a concern, a set of clinical guidelines from the British Society for Haematology on testing for heritable platelet disorders is freely available.(1)

Special Instructions

- Informed Consent for Genetic Testing
- Platelet Esoteric Testing 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

This test is designed to evaluate *MYH9*-related disorders, including May-Hegglin disorder/anomaly and Sebastian syndrome, and to be utilized for genetic confirmation of a phenotypic diagnosis of an *MYH9*-related disorder.

If testing for hereditary platelet disorders using a larger panel is desired, a 70-gene platelet disorder panel is available; order GNPLT / Platelet Disorders, Comprehensive Gene Panel, Next-Generation Sequencing, Varies.

This test is not designed to evaluate for hereditary bleeding disorders. For patients with clinical suspicion of an inherited bleeding disorder, it is important to exclude plasmatic factor deficiencies (eg, von Willebrand disease, hemophilia, or other factor deficiencies) prior to considering an inherited platelet function defect. If bleeding is the indication for testing and testing for hereditary bleeding disorders is desired, bleeding panels are available. For more information see GNBLF / Bleeding Disorders, Focused Gene Panel, Next-Generation Sequencing, Varies or GNBLC / Bleeding Disorders, Comprehensive Gene Panel, Next-Generation Sequencing, Varies.

For assessment of hereditary platelet disorders that have ultrastructural abnormalities, such as gray platelet syndrome, order PTEM / Platelet Transmission Electron Microscopic Study, Whole Blood.

For assessment of hereditary platelet disorders due to quantitative surface glycoprotein deficiencies, order PLAFL / Platelet Glycoprotein Flow Platelet Surface Glycoprotein by Flow Cytometry, Blood.

Testing for the *MYH9* gene as part of a customized panel is available. For more information see CGPH / Custom Gene Panel, Hereditary, Next-Generation Sequencing, Varies.

Targeted testing for familial variants (also called site-specific or known variants testing) is available for the *MYH9* gene. See FMTT / Familial Variant, Targeted Testing, Varies. To obtain more information about this testing option, call 800-533-1710.

Shipping Instructions

Specimen preferred to arrive within 96 hours of collection.

Necessary Information

Platelet Esoteric Testing Patient Information is required. Testing may proceed without the patient information, however, the information aids in providing a more thorough interpretation. Ordering providers are strongly encouraged to fill out the form and send with the specimen.

Specimen Required

Specimen Type: Whole blood
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.
Container/Tube:
Preferred: Lavender top (EDTA)
Acceptable: 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.**

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

Forms

1. **Platelet Esoteric Testing Patient Information is required**.
2. **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)
3. If not ordering electronically, complete, print, and send an Coagulation Test Request (T753) with the specimen.

Specimen Minimum Volume

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 & Interpretive

Clinical Information

Platelets have essential roles in primary hemostasis. Patients with either hereditary or acquired platelet disorders usually have bleeding diathesis, which can potentially be life-threatening, and may also have issues with the development and/or functioning of major organs.(2) Inherited platelet disorders can be syndromic (ie, associated with current or future development of other organ system defects) or nonsyndromic (ie, isolated to thrombocytopenia with no other organ system defects).

A reliable laboratory diagnosis of a platelet disorder can significantly impact patients' and, potentially, their family members' clinical management and outcome. Identification of an alteration that is known or suspected to cause disease aids in confirmation of the diagnosis and, potentially, provides prognostic information especially in the syndromic inherited platelet disorders.

This test evaluates the *MYH9* gene, which is associated with a variety of *MYH9*-related disorders, including May-Hegglin disorder/anomaly, Sebastian syndrome, Fechtner syndrome, Epstein syndrome, *MYH9*-related syndromic thrombocytopenia, macrothrombocytopenia and granulocyte inclusions with or without nephritis or sensorineural hearing loss, and macrothrombocytopenia with leukocyte inclusions.

The risk for developing bleeding or other phenotypic features associated with these disorders and syndromes varies. The *MYH9* gene has established bleeding, thrombocytopenia, and syndromic risk, and also expert group guidelines.(1,3-5)

It is recommended that genetic testing be offered to all patients suspected of having a heritable platelet disorder since some patients may have normal platelet laboratory testing results.(1,6) Genetic testing is integral to the conclusive diagnosis of an *MYH9*-related disorder.(5,6)

Reference Values

An interpretive report will be provided.

Interpretation

All detected variants are evaluated according to American College of Medical Genetics and Genomics recommendations.(8) 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 the 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.

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 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 healthcare 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.(8) 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. Gomez K, Anderson J, Baker P, et al: Clinical and laboratory diagnosis of heritable platelet disorders in adults and children: a British Society for Haematology Guideline. Brit J Haematol. 2021 Oct;195(1):46-72
2. Nurden AT, Freson K, Selifsohn U: Inherited platelet disorders. Haemophilia. 2012 July;18 Suppl 4:154-160
3. International Society on Thrombosis and Haemostasis: Bleeding Thrombotic and Platelet Disorder TIER1 genes. ISTH; 2018. Updated July 2022. Accessed October 6, 2022. Available at: www.isth.org/page/GinTh_GeneLists
4. Megy K, Downes K, Simeoni I, et al: Curated disease-causing genes for bleeding, thrombotic, and platelet disorders: Communication from the SSC of the ISTH. J Thromb Haemost. 2019 Aug;17(8):1253-1260
5. Bolton-Maggs PHB, Chalmers EA, Collins PW, et al: A review of inherited platelet disorders with guidelines for their management on behalf of the UKHCDO. Brit J Haematol. 2006 Dec;135(5):603-633
6. Watson SP, Lowe GC, Lordkipanidze M, Morgan NV, GAPP consortium: Genotyping and phenotyping of platelet function disorders. J Thromb Haemost. 2013 June;11 Suppl 1:351-363
7. Bury L, Megy K, Stephens JC, et al: Next-generation sequencing for the diagnosis of *MYH9*-RD: Predicting pathogenic variants. Hum Mutat. 2020 Jan;41(1):277-290
8. 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

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 *MYH9* 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 deletion-insertions less than 40 base pairs (bp), 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 *MYH9* gene.

There may be regions of the *MYH9* 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)

The reference transcript for *MYH9* is NM_002473.5. 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. Confirmation of select reportable variants may be performed by alternate methodologies based on internal laboratory criteria.

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

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

LOINC® Information

Test ID	Test Order Name	Order LOINC® Value
GNMY9	MYH9 Gene, Full Gene NGS	105332-1

Result ID	Test Result Name	Result LOINC® Value
619300	Test Description	62364-5
619301	Specimen	31208-2
619302	Source	31208-2
619303	Result Summary	50397-9
619304	Result	82939-0
619305	Interpretation	69047-9
619306	Additional Results	82939-0
619307	Resources	99622-3
619308	Additional Information	48767-8
619309	Method	85069-3
619310	Genes Analyzed	82939-0
619311	Disclaimer	62364-5
619312	Released By	18771-6