

Atypical Hemolytic Uremic Syndrome (aHUS)/Thrombotic Microangiopathy (TMA) /Complement 3 Glomerulopathy (C3G) Gene Panel, Varies

Test ID: AHUGP

Useful for:

- Providing a genetic evaluation for patients with a personal or family history suggestive of atypical hemolytic uremic syndrome (aHUS), thrombotic microangiopathy (TMA), or complement 3 glomerulopathy (C3G)
- Establishing a diagnosis of genetic aHUS, TMA, or C3G and, in some cases, allowing for appropriate management and surveillance for disease features based on the gene involved
- Identifying variants in genes encoding complement alternate pathway components and specific coagulation pathway genes known to be associated with increased risk for aHUS, TMA, and C3G allowing for predictive testing of at-risk family members
- Providing genetic information that may be considered when making treatment decisions, including duration of therapy and recurrence risk, as well as consideration of transplantation

Genetics Information:

This test utilizes next-generation sequencing to detect single nucleotide, small deletion-insertion, and copy number variants in 15 genes associated with atypical hemolytic uremic syndrome (aHUS), thrombotic microangiopathy (TMA), and complement 3 glomerulopathy (C3G): *ADAMTS13*, *C3*, *C5*[Chr9(GRCh37):g.123759950-123759973 only], *CD46* (*MCP*), *CFB*, *CFH*, *CFHR1*, *CFHR2*, *CFHR3*, *CFHR4*, *CFHR5*, *CFI*, *DGKE*, *MMACHC*, and *THBD*. See Method Description for additional details.

Identification of a pathogenic variant may assist with diagnosis, prognosis, clinical management, familial screening, and genetic counseling for aHUS, TMA, and C3G.

Reflex Tests:

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

Methods:

Sequence Capture and Amplicon-Based Next-Generation Sequencing (NGS)

Reference Values:

An interpretive report will be provided.

Ordering Guidance:

- Due to atypical hemolytic uremic syndrome genotype-phenotype complexity, targeted testing for familial variants will not be accepted without approval from the laboratory. Please call 800-533-1710 and to discuss with a genetic counselor.
- Customization of this panel and single gene analysis for any gene present on this panel are available. For more information, see CGPH / Custom Gene Panel, Hereditary, Next-Generation Sequencing, Varies

Specimen Requirements:

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

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)/Refrigerated

Minimum Volume: 1 mL

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

Specimen Stability Information: Refrigerated (preferred)/Ambient

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

Note:

Specimen preferred to arrive within 96 hours of collection.

Specimen Stability Information:

Specimen Type	Temperature	Time	Special Container
Varies	Varies		

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), including hybrid alleles formed between *CFH* and *CFHR* genes, 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.
- Genes may be added or removed based on updated clinical relevance. 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:

- At this time, 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.

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 are interpreted with caution and professional clinical judgement.
- Rarely, incidental findings or secondary findings may implicate another predisposition or presence of active disease. Incidental findings may include, but are not limited to, results related to the sex chromosomes. These findings will be carefully reviewed to determine whether they will be reported.

CPT Code:

81404

81479

Day(s) Performed: Varies

Report Available: 28 to 42 days

Questions

Contact Michelle Rath, Laboratory Technologist Resource Coordinator at 800-533-1710.