TEST ID: AHUSP

COMPLEMENT-MEDIATED ATYPICAL HEMOLYTIC-UREMIC SYNDROME (aHUS)/THROMBOTIC MICROANGIOPATHY (TMA) GENE PANEL

USEFUL FOR

- Providing a comprehensive genetic evaluation for patients with a personal or family history suggestive of complement-mediated HUS/atypical HUS (aHUS) or thrombotic microangiopathies (TMA)
- Establishing a diagnosis 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 allowing for predictive testing of at-risk family members

GENETICS TEST INFORMATION

This test includes next-generation sequencing and supplemental Sanger sequencing to evaluate for the genes listed on the panel.

Targeted testing for familial variants (also called site-specific or known mutation testing) is available for all genes on this panel. See KVAR1 / Known Variant Analysis-1 Variant; KVAR2 / Known Variant Analysis-2 Variants; or KVAR3 / Known Variant Analysis-3+ Variants. Contact Mayo Medical Laboratories to confirm the appropriate test code for targeted testing if testing for a gene not included on this panel, or if testing for more than 5 variants is needed.

CLINICAL INFORMATION

Complement-mediated hemolytic uremic syndrome, also known as atypical hemolytic uremic syndrome (aHUS), is a well-recognized disease entity characterized by complement activation in the microvasculature. Abnormalities of the alternate pathway of complement, which may be inherited (genetic) or acquired, underlie both the sporadic and familial forms of the disease and are identified in at least two-thirds (approximately 60%) of patients. Unlike many other monogenic disorders of the immune system, multiple hits may be required for disease manifestation, which may include a trigger event (transplantation, pregnancy, malignant hypertension, autoimmune disorders, sepsis, malignancy, etc), and 1 or more contributing genetic variants or haplotypes in the alternate pathway complement genes. The overall prognosis is poor with most patients developing end-stage renal disease (ESRD) or permanent kidney injury within 1 year of diagnosis despite plasma exchange (PLEX/PEX) or plasma infusion (PI) therapy. Renal transplantation in most patients is also associated with a poor prognosis with loss of the allograft. Drugs targeting the complement pathway, notably Eculizumab, have achieved success in modulating clinical remission and there are a few reports of combined liver-kidney transplants for these patients. Newer therapies are also likely to emerge over time. Individuals with genetic aHUS frequently experience relapse even after complete recovery following the presenting episode. Complement-mediated HUS presents with clinical features that are nearly identical to thrombotic thrombocytopenic purpura (TTP) and Shiga-toxin HUS (ST-HUS), making laboratory differentiation essential.
TTP is a rare clinical entity but is an important diagnosis as it is associated with very high mortality (90%) if untreated. Mortality can be reduced by early PLEX. Congenital TTP is due to genetic defects in the ADAMTS13 gene, while acquired TTP is related to autoantibodies against ADAMTS13, which reduces function. While TTP was initially characterized by thrombocytopenia, microangiopathic hemolytic anemia (MAHA), fluctuating neurological signs, renal failure and fever, the disease can present with only some of these features. The thrombotic microangiopathies (TMA) cover both aHUS and TTP and the clinical distinctions are not always clear-cut. Besides the thrombocytopenia, which is one of the key features of TMA, there is presence of schistocytes and highly increased levels of lactate dehydrogenase (LDH).

Complement-mediated HUS is considered genetic when 2 or more members of the same family are affected by the disease at least 6 months apart and exposure to a common triggering infectious agent has been excluded, or when pathogenic variants are identified in 1 or more of the genes known to be associated with aHUS, irrespective of familial history. A patient may have both autoantibodies to complement alternate pathway proteins and genetic defects in these genes.

It is important to note that certain genetic defects in these genes, eg, complement C3 (C3), may be associated with a more classic immunodeficiency phenotype with recurrent infections with encapsulated pathogens and connective tissue diseases with no evidence of aHUS/TMA.

INTERPRETATION

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

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.

CLINICAL REFERENCE