SickKids | Genome Diagnostics

COMPLEMENT BASED RENAL DISEASE

INCLUDES ATYPICAL HEMOLYTIC UREMIC SYNDROME AND MEMBRANOPROLIFERATIVE GLOMERULONEPHRITIS

Atypical Hemolytic Uremic Syndrome (aHUS) & Membranoproliferative Glomerulonephritis (MPGN) Hemolytic Uremic syndrome (HUS) is characterized by the triad of anemia, thrombocytopenia and renal dysfunction. Approximately 10% of cases of HUS are atypical. Typical HUS is preceded by diarrhea and is associated with *E. Coli* infections, whereas in atypical HUS (aHUS) diarrhea is absent and a relapsing of familial presentation is seen. MPGN is a kidney disease characterized by dense deposits within the glomerular capillary wall, associated with impaired glomerular function to filter plasma and generate a protein-free ultrafiltrate. MPGN typically presents with a hematuria and/or proteinuria, acute nephritic syndrome or nephritic syndrome. It most frequently affects children between the ages of five and 15. Both aHUS and MPGN are associated with dysfunction of the alternative complement pathway (AP) involved in innate immunity, frequently progressing to end-stage renal disease (ESRD) requiring dialysis or kidney transplantation. aHUS and MPGN are part of a spectrum of disease defined by the underlying molecular defect.

GENETICS

aHUS: A loss of function of complement regulators (CFH, CFI, CFHR5, CD46, THBD) or gain of function of activators (C3, CFB) result in over-activation of the AP. Most mutations are point mutations or small deletion/insertions. For most aHUS, the mode of inheritance is autosomal dominant where individuals carry a single copy of a mutation in one of these genes (heterozygous). However, individuals carrying two copies of the same mutation (homozygous), two copies of different mutations in the same gene (compound heterozygous), or multiple mutations in more than one aHUS-related gene have been reported. No clear genotype/phenotype correlation is currently known.

MPGN: AP components including CFH, CFHR5 and C3 have been implicated in over-activation of MPGN. Identified mutations involve point mutations or small deletions. For MPGN, individuals may be homozygous or heterozygous for one of these genes, compound heterozygous, or have multiple mutations in more than one MPGN-related gene. No clear genotype/phenotype correlation is currently known.

The inheritance in both aHUS and MPGN genes is complex. Both aHUS and MPGN have been shown to have reduced penetrance, variable expressivity, and are influenced by environmental and other genetic modifiers.

WHO SHOULD BE TESTED?

- Individuals clinically suspected of being affected with aHUS or MPGN II
- Relatives of probands with identified mutations in an aHUS or MPGN II gene
- Pregnancies at increased risk of being affected with aHUS or MPGN II

TEST METHODS

Sequence Analysis:

Bi-directional-sequencing of the exons and intronic flanking regions of seven genes shown to be associated with aHUS and MPGN. Testing is available as a panel or individual gene sequencing.

Genes	Frequency in patients	
	aHUS	MPGN
CFH	20-30%	Unknown
CD46 (MCP)	5-15%	
CFI	4-10%	
CFB	1-4%	
CFHR5	3%	
C3	2- 10%	
THBD	3– 5%	

POTENTIAL OUTCOMES & INTERPRETATION OF TEST RESULTS

Reason for referral	aHUS or MPGN mutation testing	Explanation
Diagnosis	No mutation detected	This result does not support a diagnosis of aHUS or MPGN
Diagnosis	One or more mutation detected	This result may support a diagnosis of aHUS or MPGN
Diagnosis	Variant of unknown significance	This could potentially be a disease causing mutation or could be benign and should be interpreted in the context of clinical findings, family history and other experimental data. Segregation of this variant with the disease state in other family members is available.

For More Information

GeneTests online clinical information resource –
aHUS
www.ncbi.nlm.nih.gov/books/NBK1367/
MPGN
www.ncbi.nlm.nih.gov/books/NBK1425

National Kidney Foundation
http://www.kidney.org/

Kidney Foundation of Canada
http://www.kidney.on.ca/

To locate a genetics centre near you, please visit the Canadian Association of Genetic Counsellors website at www.cagc-accg.ca or the National Society of Genetic Counsellors website at www.nsgc.org

SickKids

1. Current molecular testing may not detect all possible mutations for this disease. A negative test does not rule out the possibility of aHUS or MPGN.

2. The clinical course or severity of symptoms cannot be predicted by molecular analysis.

3. Test results should be interpreted in the context of clinical findings, family history and other laboratory data.

4.This test was developed and its performance characteristics validated by the Genome Diagnostics Laboratory at the Hospital for Sick Children. It has not been cleared or approved by the U.S. Food and Drug Administration. The FDA has determined that such clearance or approval is not necessary. This test is used for clinical purposes.