Agammaglobulinemia Panel

Indications for Ordering

Confirm suspected agammaglobulinemia in individual with clinical symptoms

Test Description

- Targeted capture of all coding exons and intron/exon boundaries followed by massively parallel sequencing
  - Reported variants are confirmed by Sanger sequencing
- Deletion/duplication analysis by tiled, custom-designed comparative genomic hybridization (CGH) array

Tests to Consider

Primary test

Agammaglobulinemia Panel, Sequencing (9 Genes) and Deletion/Duplication (6 Genes) 2011151

- Preferred test for individuals with clinical phenotype of agammaglobulinemia

Related tests

Initial screening for immunodeficiency

- CBC with Platelet Count and Automated Differential 0040003
- Lymphocyte Subset Panel 7 – Congenital Immunodeficiencies 0095899
- Lymphocyte Antigen and Mitogen Proliferation Panel with Cytokine Response 2013117
- Immunoglobulins (IgA, IgG, IgM), Quantitative 0050630
- Familial Mutation, Targeted Sequencing 2001961

Initial screening for suspected primary agammaglobulinemia

- Bruton Tyrosine Kinase (BTK) Protein Expression by Flow Cytometry 2012002

Disease Overview

Prevalence

- X-linked agammaglobulinemia – ~1/250,000-700,000
- Autosomal inherited agammaglobulinemia – rare

Age of onset – usually within the first 2 years of life

Symptoms

- Recurrent or chronic infections
  - Encapsulated pyogenic bacteria
  - Enteroviruses
- Neutropenia
- Pneumonia/empyema
- Gastroenteritis
- Otitis media
- Meningitis
- Sepsis

Genetics

Genes – see table for genes tested and for gene-specific information

Mutations

- Mutations in multiple genes appear to cause overlapping phenotypes for agammaglobulinemia
- Other genetic and/or environmental factors may influence severity of clinical phenotype

Test Interpretation

Clinical sensitivity – ~90%

Results

- Positive
  - Two pathogenic mutations on opposite chromosomes detected in a gene with autosomal recessive (AR) inheritance
    - Confirms diagnosis of agammaglobulinemia
  - Single pathogenic mutation detected in an X-linked gene in males or in an autosomal dominant (AD) gene in males or females
    - Confirms diagnosis of agammaglobulinemia
  - Detection of one pathogenic mutation in gene with AR inheritance
    - Individual is a carrier
  - Detection of one pathogenic mutation in an X-linked gene in females
    - Individual is a carrier
- Negative – no pathogenic mutation detected
  - Reduces, but does not exclude, a diagnosis of agammaglobulinemia
- Inconclusive – variants of uncertain clinical significance may be identified

Limitations

- Not determined or evaluated
  - Mutations in genes not included on the panel
  - Deep intronic and regulatory region mutations
  - Breakpoints for large deletions/duplications
  - Translocations
- Deletions/duplications will not be detected in
  - *LRRC8A* gene
  - *PIK3R1* gene
  - *SH2D1A* gene
- Small deletions or insertions may not be detected
- Diagnostic errors can occur due to rare sequence variations
- Lack of detectable gene mutation does not exclude diagnosis of agammaglobulinemia

Reference

Conley ME, et al. Primary B cell immunodeficiencies: comparisons and contrasts. Annu Rev Immnunol. 2009;27:199-227

Gene Symbol	Gene Name	NM #	OMIM #	Phenotype/Disorder	Inh.*
BLNK	B-cell linker	013314	604515	Agammaglobulinemia	AR
BTK	Bruton agammaglobulinemia tyrosine kinase	000061	300300	Agammaglobulinemia and isolated growth hormone deficiency X-linked agammaglobulinemia	XL
CD79A	CD79A antigen, Iga	001783	112205	Agammaglobulinemia	AR
CD79B	CD79B molecule, Igb	000626	147245	Agammaglobulinemia	AR
IGHM	Immunoglobulin heavy constant mu	cDNA:X17115	147020	Agammaglobulinemia	AR
IGLL1	Immunoglobulin lambda-like polypeptide 1, 15	020070	146770	Agammaglobulinemia	AR
LRRC8A	Leucine rich repeat containing 8 family, member A	019594	608360	Agammaglobulinemia	AD
PIK3R1	Phosphoinositide-3-kinase, regulatory subunit, polypeptide 1 (p85 alpha)	181523	171833	Agammaglobulinemia	AR
SH2D1A	SH2 domain protein 1A, Duncan's disease (lymphoproliferative syndrome)	002351	300490	X-linked lymphoproliferative syndrome	XL

*Inh. = inheritance, AD = autosomal dominant, AR = autosomal recessive, XL = X-linked