# Hyper IgM Syndrome Panel

## Indications for Ordering

Confirm suspected hyper IgM syndrome 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

Hyper IgM Syndrome Panel, Sequencing (12 Genes) and Deletion/Duplication (10 Genes) 2011154

- Preferred test for individuals with clinical phenotype of hyper IgM syndrome

### Related tests

Initial screening for immunodeficiency

- CBC with Platelet Count and Automated Differential 0040003
- Lymphocyte Subset Panel 7 - Congenital Immunodeficiencies 0095899
- B-Cell Memory and Naive Panel 2008901
- Lymphocyte Antigen and Mitogen Proliferation Panel with Cytokine Response 2013117
- Immunoglobulins (IgA, IgG, IgM), Quantitative 0050630
- Familial Mutation, Targeted Sequencing 2001961

## Disease Overview

### Prevalence

- X-linked hyper IgM syndrome – 1-2/million
- Autosomal inherited hyper IgM syndrome – rare

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

### Symptoms

- Unusual, opportunistic, or severe infections
  - Most common organisms
    - *Pneumocystis jiroveci*
    - *Histoplasma capsulatum*
    - *Cryptosporidium* spp
    - *Cryptococcus neoformans*
  - Sites most commonly involved
    - Gastrointestinal
      - Oral ulcers/gingivitis/stomatitis
    - Respiratory
    - Skin
    - ENT – otitis media
- Nonspecific
  - Failure to thrive
  - Lymphadenopathy
  - Tonsillar enlargement
  - Neutropenia
- Autoimmune conditions

## Genetics

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

### Mutations

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

## Test Interpretation

**Clinical sensitivity** – ~75-80%

**Results**

- Positive
  - Two pathogenic mutations detected on opposite chromosomes in a gene with autosomal recessive (AR) inheritance
    - Confirms diagnosis of hyper IgM syndrome
  - One pathogenic mutation detected in an X-linked gene in males or an autosomal dominant gene in males or females
    - Confirms diagnosis of hyper IgM syndrome
  - One pathogenic mutation detected in an AR gene
    - Individual is a carrier
  - One pathogenic mutation detected in an X-linked gene in females
    - Individual is a carrier
- Negative – no pathogenic mutation detected
  - Reduces, but does not exclude, a diagnosis of hyper IgM syndrome
- 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
  - *IKBKG* gene
  - *PIK3CD* gene
- Small deletions or insertions may not be detected
- Diagnostic errors can occur due to rare sequence variations
- Lack of a detectable gene mutation does not exclude a diagnosis of hyper IgM syndrome

| Gene Symbol | Gene Name | NM # | OMIM # | Phenotype/Disorder | Inh.* |
|---|---|---|---|---|---|
| *AICDA* | Activation-induced cytidine deaminase | NM_020661 | 605257 | Immunodeficiency with hyper IgM, type 2 | AR or AD |
| *ATM* | Ataxia telangiectasia mutated (includes complementation groups A, C and D) | NM_000051 | 607585 | Ataxia telangiectasia | AR |
| *BTK* | Bruton agammaglobulinemia tyrosine kinase | NM_000061 | 300300 | Agammaglobulinemia and isolated growth hormone deficiency<br>X-linked agammaglobulinemia | XL |
| *CD40* | cd40 antigen | NM_001250 | 109535 | Immunodeficiency with hyper IgM | AR |
| *CD40LG* | CD40 ligand (TNF superfamily, member 5, hyper IgM syndrome, TNFSF5) | NM_000074 | 300386 | Immunodeficiency with X-linked hyper IgM | XL |
| *IKBKG* | Inhibitor of kappa light polypeptide gene enhancer in B cells, kinase gamma, NEMO | NM_001099857 | 300248 | Hypohidrotic or anhidrotic ectodermal dysplasia with lymphedema and immune deficiency<br>Incontinentia pigmenti<br>Recurrent isolated invasive pneumococcal disease<br>Immunodeficiency 33 | XL |
| *MRE11A* | Meiotic recombination 11 homologue A | NM_005591 | 600814 | Ataxia-telangiectasia-like disorder | AR |
| *NBN/NBS1* | Nibrin | NM_002485 | 602667 | Nijmegen breakage syndrome | AR |
| *NFKBIA* | Nuclear factor of kappa light polypeptide gene enhancer in B-cell inhibitors, alpha | NM_020529 | 164008 | Ectodermal dysplasia, anhidrotic, with T-cell immunodeficiency | AD |
| *PIK3CD* | Phosphoinositide-3-kinase, catalytic, delta polypeptide | NM_005026 | 602839 | Immunodeficiency 14 | AD |
| *RAG2* | Recombination activating gene 2 | NM_000536 | 179616 | SCID, T-cell/B-cell negative, NK-cell positive<br>Omenn syndrome<br>Combined cellular and humoral immune defects with granulomas | AR |
| *UNG* | Uracil DNA glycosylase | NM_080911 | 191525 | Immunodeficiency with hyper IgM | AR |

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