

Using Genetic Testing to Diagnose Defects in B-Cell Development and Function

Hyper IgM Syndrome, X-linked Agammaglobulinemia, Common Variable Immunodeficiency

Indications:

- Recurrent, persistent, or severe bacterial infections
- Low serum immunoglobulin levels
- Family history of recurrent infections or family history of XLA, HIGM, or CVID

Benefits:

- Genetic testing can confirm a diagnosis in the proband and allow early diagnosis in family members. Early diagnosis is critical since complications are minimized if treatment begins before serious infections develop.¹⁻⁴
- Several monogenic causes have been identified for XLA, HIGM, and CVID. By identifying the exact molecular cause, genetic testing can facilitate selection of the most appropriate therapy and may clarify the prognosis.

Background:

- B-cell deficiency is characterized by recurrent, severe bacterial infections and low serum immunoglobulin levels in the presence of normal T-cell levels.
 - **X-linked Agammaglobulinemia (XLA)** is distinguished by deficiency in all classes of immunoglobulins and a reduction in the number of circulating B cells.¹
 - **Hyper IgM (HIGM) Syndromes** present with normal or elevated levels of IgM and a virtual absence of all other antibody isotypes in the presence of normal B-cell levels. Depending on the underlying genetic cause, there may also be a defect in T-cell mediated immunity, giving rise to more severe symptoms.^{2,3}
 - **Common Variable Immunodeficiency (CVID)** is characterized by reduced levels of IgA, IgG, and/or IgM, with normal B-cell levels. Diagnosis of CVID requires exclusion of other causes of antibody deficiency, including XLA and HIGM.⁴
- XLA, HIGM, and CVID are typically treated with intravenous immunoglobulin (IVIG) and aggressive use of antibiotics.¹⁻⁴ Depending on the genetic cause, bone marrow transplantation may also be warranted.^{2,5}

References: 1. Conley ME (2005) *Immunol Rev* 203:216-234. 2. Durandy A et al (2005) *Immunol Rev* 203: 67-79. 3. Lougaris V et al (2005) *Immunol Rev* 203:48-66 4. Di Renzo M et al (2004) *Clin Exp Med* 3:211-217 5. Notarangelo LD et al (1992) *Immunodeficiency Rev* 3:101-121

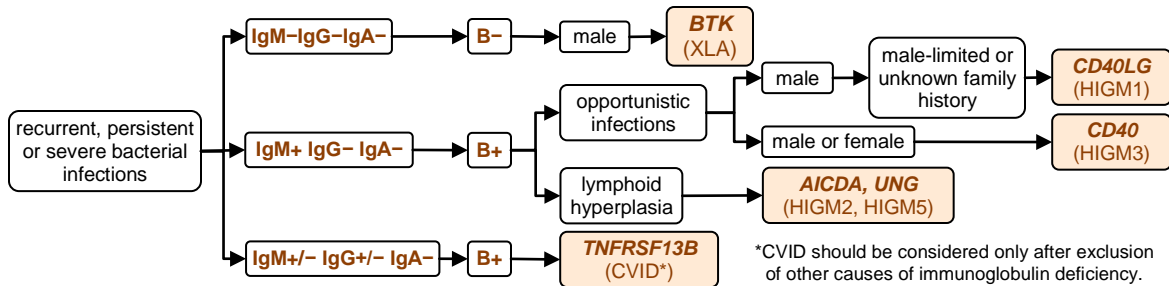
Ordering Information: Please see other side.

Ordering Information for B-Cell Deficiency Testing: Hyper IgM Syndrome (HIGM), X-Linked Agammaglobulinemia (XLA), Common Variable Immunodeficiency (CVID)

Indications for Testing

- Recurrent, persistent, or severe bacterial infections
- Low serum immunoglobulin levels
- Family history of recurrent or persistent infections, or a family history of XLA, HIGM, or CVID

Guidelines for Test Selection



Ordering Information for Single Gene Tests

Test-Specific Indication	Indicated Test	Test Code
• IgM+ IgG- IgA-; B+	AICDA (HIGM2)	100101
• IgM+ IgG- IgA-; B+	UNG (HIGM5)	100102
• IgM+ IgG- IgA-; B+	CD40 (<i>TNFRSF5</i>) (HIGM3)	100103
• IgM+ IgG- IgA-; B+	CD40LG (<i>TNFRSF5</i>) (HIGM1)	100104
• IgM- IgG- IgA-; B-	BTK (XLA)	100201
• IgM ^{+/+} - IgG ^{+/+} - IgA ⁺ ; B ⁺	TNFRSF13B (<i>TAC1</i>) (CVID)	100701
• onset of symptoms usually in older patients		

Ordering Information for Multi-Gene Panels**

• IgM+ IgG- IgA-; B+	AICDA, UNG (HIGM2/5)	100199
• IgM+ IgG- IgA-; B+	AICDA, UNG, CD40 (HIGM, autosomal recessive)	100198
• IgM+ IgG- IgA-; B+	AICDA, UNG, CD40, CD40LG (HIGM)	100197

**For multi-gene panels, a summary report will be issued in addition to an abbreviated report for each individual gene.

Family Testing (single amplicon)

Family Testing is available for all genes. Please contact Client Services at 1-866-647-0735 for requirements.

Test Methodology

- Amplification by polymerase chain reaction (PCR); sequencing of entire protein-coding region

NOTE: Specimens must be accompanied by a completed consent form. In the case of family tests (ie, known mutations), a copy of the result of the first patient tested in the family (the index case) must be submitted unless that test was performed at Correlagen. Other family members are subsequently tested for the specific mutation found in the first patient tested.

For test information, sample requirements, or to request a sample shipping kit, please contact Client Services at 1-866-647-0735 or visit us on the web at www.correlagen.com.