

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

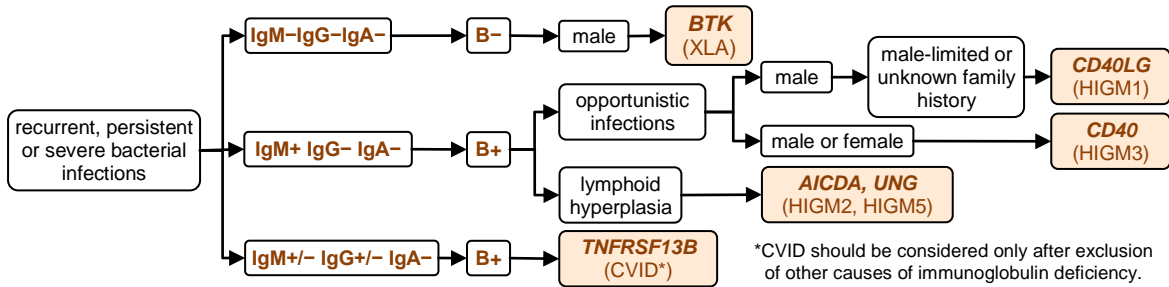
Ordering Information: Please see other side.

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	CPT Codes	Test Code
• IgM+ IgG-IgA-; B+	AICDA (HIGM2)	83891(1) 83892(1) 83898(5) 83904(10) 83909(10) 83912(1)	100101
• IgM+ IgG- IgA-; B+	UNG (HIGM5)	83891(1) 83892(1) 83898(7) 83904(14) 83909(14) 83912(1)	100102
• IgM+ IgG- IgA-; B+	CD40 (TNFRSF5) (HIGM3)	83891(1) 83892(1) 83898(9) 83904(18) 83909(18) 83912(1)	100103
• IgM+ IgG- IgA-; B+ • X-linked	CD40LG (TNFRSF5) (HIGM1)	83891(1) 83892(1) 83898(6) 83904(12) 83909(12) 83912(1)	100104
• IgM- IgG- IgA-; B- • X-linked	BTK (XLA)	83891(1) 83892(1) 83898(18) 83904(36) 83909(36) 83912(1)	100201
• IgM ^{+/-} IgG ^{+/-} IgA ⁻ ; B ⁺ • onset of symptoms usually in older patients	TNFRSF13B (TAC1) (CVID)	83891(1) 83892(1) 83898(5) 83904(10) 83909(10) 83912(1)	100701

Ordering Information for Multi-Gene Panels**

• IgM+ IgG- IgA-; B+	AICDA, UNG (HIGM2/5)	83891(1) 83892(1) 83898(12) 83904(24) 83909(24) 83912(3)	100199
• IgM+ IgG- IgA-; B+	AICDA, UNG, CD40 (HIGM, autosomal recessive)	83891(1) 83892(1) 83898(21) 83904(42) 83909(42) 83912(4)	100198
• IgM+ IgG- IgA-; B+	AICDA, UNG, CD40, CD40LG (HIGM)	83891(1) 83892(1) 83898(27) 83904(54) 83909(54) 83912(5)	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)

(applies to all genes)	83891(1) 83892(1) 83898(1) 83904(2) 83909(2) 83912(1)	use single-gene test code
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Test Methodology and Sample Requirements

- Amplification by polymerase chain reaction (PCR); sequencing of entire protein-coding region
- For blood samples:
 - 2ml whole blood in EDTA tube (lavender top)
 - Samples can be stored briefly at 4°C, but should be shipped on day of collection.
- For buccal swab samples:
 - Please contact client services at 1-866-647-0735 for instructions.
- All sample types should be shipped overnight at room temperature.
- To request a sample shipping kit, please call 1-866-647-0735.

Turn-around Times

Turn-around times typically range from 7 to 21 days of receipt of sample and all required forms, but may vary depending on test volume and test-specific technical difficulties. Current TATs are posted on our website. Please schedule patient follow-up appointments for discussion of test results conservatively at 6 weeks.

**For more information, please contact Correlagen Diagnostics, Inc., at 1-866-647-0735
or visit us on the web at www.correlagen.com.**