U.S. National Library of Medicine
National Center for Biotechnology Information

NLM Citation: Dunn CP, de la Morena MT. X-Linked Hyper IgM Syndrome. 2007 May 31 [Updated 2020 Feb 20]. In: Adam MP, Feldman J, Mirzaa GM, et al., editors. GeneReviews® [Internet]. Seattle (WA): University of Washington, Seattle; 1993-2024.
Bookshelf URL: https://www.ncbi.nlm.nih.gov/books/

X-Linked Hyper IgM Syndrome

Synonyms: HIGM1, X-Linked Hyper-IgM Immunodeficiency (XHIGM)

Clinton P Dunn, MD[1] and M Teresa de la Morena, MD[1]

Created: May 31, 2007; Updated: February 20, 2020.

Summary

Clinical characteristics

X-linked hyper IgM syndrome (HIGM1), a disorder of abnormal T- and B-cell function, is characterized by low serum concentrations of IgG, IgA, and IgE with normal or elevated serum concentrations of IgM. Mitogen proliferation may be normal, but NK- and T-cell cytotoxicity can be impaired. Antigen-specific responses are usually decreased or absent. Total numbers of B cells are normal but there is a marked reduction of class-switched memory B cells. Defective oxidative burst of both neutrophils and macrophages has been reported. The range of clinical findings varies, even within the same family. More than 50% of males with HIGM1 develop symptoms by age one year, and more than 90% are symptomatic by age four years. HIGM1 usually presents in infancy with recurrent upper- and lower-respiratory tract bacterial infections, opportunistic infections including *Pneumocystis jirovecii* pneumonia, and recurrent or protracted diarrhea that can be infectious or noninfectious and is associated with failure to thrive. Neutropenia is common; thrombocytopenia and anemia are less commonly seen. Autoimmune and/or inflammatory disorders (such as sclerosing cholangitis) as well as increased risk for neoplasms have been reported as medical complications of this disorder. Significant neurologic complications, often the result of a CNS infection, are seen in 5%-15% of affected males. Liver disease, a serious complication of HIGM1 once observed in more than 80% of affected males by age 20 years, may be decreasing with adequate screening and treatment of *Cryptosporidium* infection.

Diagnosis/testing

The diagnosis of X-linked hyper IgM syndrome is established in a male proband with typical clinical and laboratory findings and a hemizygous pathogenic variant in *CD40LG* identified by molecular genetic testing.

Management

Treatment of manifestations: Hematopoietic stem cell transplantation (HSCT) (the only curative treatment currently available), ideally performed before age ten years, prior to evidence of organ damage; immunoglobulin replacement therapy (either intravenous or subcutaneous); appropriate antimicrobial therapy for acute

Author Affiliation: 1 University of Washington, Seattle Children's Hospital, Seattle, Washington; Email: cpdunn08@uw.edu; Email: mariateresa.delamorena@seattlechildrens.org.

infections; antimicrobial prophylaxis for opportunistic infection against *Pneumocysitis jirovecii* pneumonia; recombinant granulocyte colony-stimulating factor for chronic neutropenia; immunosuppressants for autoimmune disorders.

Agents/circumstances to avoid: Areas that place individual at risk of contracting *Cryptosporidium* including pools, lakes, ponds, or certain water sources; drinking unpurified or unfiltered water; live vaccines such as rotavirus, MMR, varicella, live attenuated polio, and BCG.

Surveillance: At least annually: CBC with differential to monitor for cytopenias, testing of IgG levels and lymphocyte subpopulations, pulmonary function tests after age seven years. Regular assessment of liver function, consider abdominal imaging; as well as polymerase chain reaction-based testing for the presence of enteric pathogens including *Cryptosporidium*. Monitor growth and general health with a low threshold for lymph node biopsy, given elevated oncologic risk.

Evaluation of relatives at risk: It is appropriate to clarify the genetic status of newborn at-risk relatives of an affected individual in order to identify as early as possible those who would benefit from early diagnosis and prompt initiation of treatment and prevention of infections.

Genetic counseling

By definition, X-linked hyper IgM syndrome (HIGM1) is inherited in an X-linked manner. Affected males transmit the pathogenic variant to all their daughters and none of their sons. Women with a *CD40LG* pathogenic variant have a 50% chance of transmitting the pathogenic variant in each pregnancy. Males who inherit the pathogenic variant will be affected. Female who inherit the pathogenic variant will typically be asymptomatic but may have a range of clinical manifestation depending on X-chromosome inactivation. Once the *CD40LG* pathogenic variant has been identified in an affected family member, heterozygote testing for at-risk female relatives, prenatal testing for a pregnancy at increased risk, and preimplantation genetic testing for HIGM1 are possible.

Diagnosis

Suggestive Findings

X-linked hyper IgM syndrome (HIGM1) **should be suspected** in any male presenting with *Pneumocystis jirovecii* pneumonia, persistent *Cryptosporidium* diarrhea, recurrent upper- and lower-respiratory tract bacterial infections, neutropenia, sclerosing cholangitis, and associated bile duct tumors with the following laboratory abnormalities:

- Absent or low serum concentrations of IgG and IgA
- Normal or elevated serum concentrations of IgM
- Normal:
  - Number and distribution of T, B, and NK lymphocyte subsets
  - T-cell proliferation in response to mitogens
- Decreased expression of CD40L on the surface of activated CD4 cells (not universal)

Establishing the Diagnosis

The diagnosis of HIGM1 **is established** in a male proband with typical clinical and laboratory findings by identification of a hemizygous pathogenic (or likely pathogenic) variant in *CD40LG* on molecular genetic testing (see Table 1).

The diagnosis of HIGM1 is extremely rare in a female, as heterozygous females are typically asymptomatic unless there is skewed X-chromosome inactivation (see Clinical Description).

Note: (1) Per ACMG/AMP variant interpretation guidelines, the terms "pathogenic variant" and "likely pathogenic variant" are synonymous in a clinical setting, meaning that both are considered diagnostic and can be used for clinical decision making [Richards et al 2015]. Reference to "pathogenic variants" in this section is understood to include likely pathogenic variants. (2) Identification of a hemizygous *CD40LG* variant of uncertain significance does not establish or rule out the diagnosis.

Molecular genetic testing approaches can include a combination of **gene-targeted testing** (single-gene testing, multigene panel) and **comprehensive genomic testing** (exome sequencing, exome array, genome sequencing) depending on the phenotype and the family history.

Gene-targeted testing requires that the clinician determine which gene(s) are likely involved, whereas genomic testing does not. Because the phenotype of X-linked hyper IgM syndrome is broad, individuals with the distinctive findings described in Suggestive Findings are likely to be diagnosed using gene-targeted testing (see Option 1), whereas those with a phenotype indistinguishable from many other inherited disorders with immunodeficiency are more likely to be diagnosed using genomic testing (see Option 2).

Option 1

When the phenotypic and laboratory findings suggest the diagnosis of HIGM1 syndrome, molecular genetic testing approaches can include **single-gene testing** or use of a **multigene panel**:

- **Single-gene testing.** Sequence analysis of *CD40LG* is performed first to detect small intragenic deletions/insertions and missense, nonsense, and splice site variants. Note: Depending on the sequencing method used, single-exon, multiexon, or whole-gene deletions/duplications may not be detected. If no variant is detected by the sequencing method used, the next step is to perform gene-targeted deletion/duplication analysis to detect exon and whole-gene deletions or duplications.
- **An immunodeficiency multigene panel** that includes *CD40LG* and other genes of interest (see Differential Diagnosis) is most likely to identify the genetic cause of the condition while limiting identification of variants of uncertain significance and pathogenic variants in genes that do not explain the underlying phenotype. Note: (1) The genes included in the panel and the diagnostic sensitivity of the testing used for each gene vary by laboratory and are likely to change over time. (2) Some multigene panels may include genes not associated with the condition discussed in this *GeneReview*. (3) In some laboratories, panel options may include a custom laboratory-designed panel and/or custom phenotype-focused exome analysis that includes genes specified by the clinician. (4) Methods used in a panel may include sequence analysis, deletion/duplication analysis, and/or other non-sequencing-based tests.

  For this disorder a multigene panel that also includes deletion/duplication analysis is recommended (see Table 1).

  For an introduction to multigene panels click here. More detailed information for clinicians ordering genetic tests can be found here.

Option 2

When the phenotype is indistinguishable from many other inherited disorders characterized by immunodeficiency, **comprehensive genomic testing** (which does not require the clinician to determine which gene[s] are likely involved) is the best option. **Exome sequencing** is most commonly used; **genome sequencing** is also possible.

If exome sequencing is not diagnostic, **exome array** (when clinically available) may be considered to detect (multi)exon deletions or duplications that cannot be detected by sequence analysis.

For an introduction to comprehensive genomic testing click here. More detailed information for clinicians ordering genomic testing can be found here.

Table 1. Molecular Genetic Testing Used in X-Linked Hyper IgM Syndrome (HIGM1)

Gene [1]	Method	Proportion of Probands with a Pathogenic Variant [2] Detectable by Method
CD40LG	Sequence analysis [3]	85%-95% [4]
	Gene-targeted deletion/duplication analysis [5]	5%-15% [4]

1. See Table A. Genes and Databases for chromosome locus and protein.
2. See Molecular Genetics for information on variants detected in this gene.
3. Sequence analysis detects variants that are benign, likely benign, of uncertain significance, likely pathogenic, or pathogenic. Variants may include small intragenic deletions/insertions and missense, nonsense, and splice site variants; typically, exon or whole-gene deletions/duplications are not detected. For issues to consider in interpretation of sequence analysis results, click here.
4. Lee et al [2005], Prasad et al [2005], Cabral-Marques et al [2014], Leven et al [2016]
5. Gene-targeted deletion/duplication analysis detects intragenic deletions or duplications. Methods used may include a range of techniques such as quantitative PCR, long-range PCR, multiplex ligation-dependent probe amplification (MLPA), and a gene-targeted microarray designed to detect single-exon deletions or duplications.

Additional Confirmatory Testing

Measurement by flow cytometry of CD40 ligand (CD40L) protein expression after in vitro stimulation of T cells. In the resting state, only a low level of CD40L protein expression is seen on normal CD4+ T cells. After in vitro stimulation:

- Controls show increased expression (up-regulation) of CD40L protein in the majority of CD4+ T cells which is determined by monoclonal anti-human IgG to CD40L.

  Note: Infants younger than age six months may not express normal amounts of CD40L protein [Gilmour et al 2003].

- Persons with HIGM1 do not show increased expression of CD40L protein in CD4+ T cells.

NOTE: This testing should not be used as the only diagnostic test when HIGM1 is suspected. Up to 32% of individuals with HIGM1 may have normal extracellular domains of CD40L detected by this laboratory measure, which uses CD40L binding; but the intracellular signaling pathway from CD40L is nonfunctional, and thus genetic testing is required for diagnosis [Lee et al 2005].

Clinical Characteristics

Clinical Description

X-linked hyper IgM syndrome (HIGM1), a disorder of abnormal T- and B-cell function, is characterized by low serum concentrations of IgG, IgA, and IgE and normal or elevated serum concentrations of IgM. HIGM1 is due to defects or deficiencies in the CD40L protein that affect T cell communication with B lymphocytes. Mitogen proliferation may be normal but NK- and T-cell cytotoxicity can be impaired. Antigen-specific responses are usually decreased or absent.

Males

The range of clinical findings varies, even within the same family. More than 50% of males with HIGM1 develop symptoms by age one year, and more than 90% are symptomatic by age four years [Winkelstein et al 2003].

Presentation. HIGM1 usually presents in infancy with recurrent upper- and lower-respiratory tract bacterial infections, opportunistic infections including *Pneumocystis jirovecii* pneumonia, and recurrent or protracted diarrhea that can be infectious or noninfectious and is associated with failure to thrive. Neutropenia is common; thrombocytopenia and anemia are also (though less commonly) seen. Autoimmune and/or inflammatory disorders (such as sclerosing cholangitis) as well as increased risk for neoplasms have been reported as medical complications of this disorder [Lee et al 2005, Leven et al 2016, de la Morena et al 2017].

Infection. Increased susceptibility to recurrent bacterial infections consisting of upper- and lower-respiratory tract infections is seen in 75%-80% of affected individuals (typically streptococcus pneumonia and pseudomonas), otitis in 42%, and sinusitis in 36% [Leven et al 2016]. Susceptibility to invasive fungal infections (primarily *Candida*, *Cryptococcus*, and *Histoplasma*) is also increased. Boys with HIGM1 are also at a significant risk for opportunistic infections from *Pneumocystis jirovecii* (PJP; formerly known as *Pneumocystis carinii)* and gastrointestinal infection with *Cryptosporidium parvum*.

Pneumocystis jirovecii pneumonia is the first clinical symptom of HIGM1 in more than 40% of infants with the disorder and is shown as the pathogenic organism in roughly 30% of individuals with HIGM1 [Levy et al 1997, Lee et al 2005, de la Morena 2016, Leven et al 2016] and accounts for 10%-15% of the mortality associated with HIGM1 [Levy et al 1997, Winkelstein et al 2003].

The presentation of HIGM1 across different ethnic backgrounds and in different countries has been shown to be consistent in the infectious organisms at present across all individuals with HIGM1 but they are also at risk for the pathogens that are endemic to their specific region [Cabral-Marques et al 2014, Wang et al 2014, Rawat et al 2018, Tafakori Delbari et al 2019].

Gastrointestinal manifestations. Chronic diarrhea is the most frequent GI complication of HIGM1, occurring in approximately 20%-30% of affected males [Winkelstein et al 2003, Leven et al 2016]. Recurrent or protracted diarrhea may result from infection with *Cryptosporidium parvum* or other microorganisms; however, in at least 50% of males with recurrent or protracted diarrhea, no infectious agent can be detected [Winkelstein et al 2003, Leven et al 2016]. Poor growth is a serious complication of chronic diarrhea. Additionally, aphthous ulcers can be present in 21% of affected males [Leven et al 2016].

Hematologic and immunologic abnormalities. Neutropenia occurs in roughly 45%-50% of males with HIGM1, with anemia seen in 10%-15% and thrombocytopenia in 5% [Levy et al 1997, Lee et al 2005, Cabral-Marques et al 2014, Leven et al 2016]. Severe aplastic anemia secondary to parvovirus B19 has been found, but was reported as the initial finding in individuals with a milder phenotype and later age of presentation [Seyama et al 1998, Leven et al 2016, de la Morena 2016].

The total number of B cells in circulation is normal, however, there is a marked reduction of class-switched memory B cells [Agematsu et al 1998]. Furthermore, some individuals with HIGM1 may show progressive loss of B and NK cell populations over time, which can contribute to the increased morbidity [Lougaris et al 2018]. Defective oxidative burst of both neutrophils and macrophages have been reported – the result of impaired interaction between neutrophils, macrophages and, activated T lymphocytes through CD40 and CD40LG [Cabral-Marques et al 2018].

Histologic examination of lymph nodes shows absence of germinal center formation.

Neurologic involvement. Significant neurologic complications, often the result of a CNS infection, are seen in 5%-15% of males with HIGM1 [Levy et al 1997, Cabral-Marques et al 2014, Leven et al 2016]. However, in at least half of affected individuals a specific infectious agent cannot be isolated [Winkelstein et al 2003].

Hepatobiliary disease. Liver disease, a serious complication of HIGM1, historically was observed in more than 80% of affected males by age 20 years [Hayward et al 1997] but with adequate screening and treatment of *Cryptosporidium* infections, that number may now be lower [Leven et al 2016]. Hepatitis and sclerosing cholangitis occur in 6%-10% of affected individuals. CD40, the receptor to which CD40Ligand (CD40L) binds, has been shown to be expressed on bile duct epithelium; chronic infection with *Cryptosporidium* or other inflammatory changes are thought to contribute to sclerosing cholangitis and malignant transformation [Hayward et al 1997, de la Morena 2016, Leven et al 2016].

Oncologic disease. Malignancies occur in approximately 5% of individuals with HIGM1 and are associated with high mortality [Winkelstein et al 2003, de la Morena 2016, Leven et al 2016]. Malignancies reported in individuals with HIGM1 include neuroendocrine tumors of the GI tract, colon cancer, bile duct carcinomas, hepatocellular carcinomas, hepatoma, adrenal adenomas, and adenocarcinomas of the liver and gall bladder [Hayward et al 1997, Winkelstein et al 2003, Filipovich & Gross 2004, Erdos et al 2008, Leven et al 2016, Nicolaides & de la Morena 2017].

Males with HIGM1 are also at increased risk for acute myelogenous leukemia and lymphoma, particularly Hodgkin disease associated with Epstein-Barr virus infection [Filipovich & Gross 2004].

Other (rarely) reported complications of HIGM1 include autoimmune retinopathy, cutaneous granulomas, and disseminated cutaneous warts [Gallerani et al 2004, Schuster et al 2005, Ho et al 2018].

Life span. The current reported median survival time from diagnosis is 25 years [de la Morena et al 2017]. *Pneumocystis jirovecii* pneumonia in infancy, liver disease, and malignancies in adolescence or young adulthood are important contributors to mortality [Levy et al 1997, Winkelstein et al 2003, de la Morena 2016, Leven et al 2016].

Hematopoietic stem cell transplant (HSCT) is the only curative therapy available for HIGM1. In a retrospective series of 130 affected individuals who had undergone HSCT, overall survival, event-free survival, and disease-free survival rates were respectively 78.2%, 58.1%, and 72.3% five years post HSCT [Ferrua et al 2019].

Heterozygous Females

Typically, heterozygous females are asymptomatic but on immunologic testing have been shown to have reduced expression of CD40L on activation of CD4+ T lymphocytes. Those females with more dramatic reduction in circulating lymphocytes with CD40L due to skewed X-chromosome inactivation can have a presentation similar to HIGM1 or common variable immunodeficiency [Hollenbaugh et al 1994, de Saint Basile et al 1999, Lobo et al 2002].

Genotype-Phenotype Correlations

Males with HIGM1 show remarkable variability in clinical symptoms.

No specific genotype-phenotype correlations for *CD40LG* have been identified [Notarangelo & Hayward 2000, Prasad et al 2005]. However, the p.Thr254Met and p.Arg11Ter pathogenic variants have been reported in unrelated families with milder and later-onset disease [Seyama et al 1998, Lee et al 2005]. Whether or not this is a true association needs to be evaluated with study of additional families with the pathogenic variant.

Prevalence

The estimated prevalence of HIGM is 1:1,000,000 males [Winkelstein et al 2003] with nearly 75% of these individuals having HIGM1 [Leven et al 2016].

HIGM1 has been reported in families of European, African, and Asian descent; thus, no evidence exists for a racial or ethnic predilection.

Genetically Related (Allelic) Disorders

Duplication of *CD40LG* has been reported in a boy and his mother who both presented with autoimmune diseases [Le Coz et al 2018].

Differential Diagnosis

Table 2. Disorders to Consider in the Differential Diagnosis of X-Linked Hyper IgM Syndrome (HIGM1)

Gene(s)	Differential Disorder	MOI	Clinical Features of Differential Disorder	
			Overlapping w/HIGM1	Distinguishing from HIGM1
AICDA (*AID*)	HIGM2 (OMIM 605258)	AR	Abnormalities in B-cell differentiation → recurrent URTI, LRTI, GI infections	• Opportunistic infections rare • Lymphoid hyperplasia common; incl: hepatomegaly, splenomegaly, giant germinal centers, follicular hyperplasia. • Autoimmunity w/hemolytic anemia more common [1] Note: Clinical course milder in HIGM4 than in HIGM2 [2]
	HIGM4 (OMIM 608184)	AD [3]	• Recurrent URTI, LRTI • ↓ production of IgG, abnormalities in B cell differentiation [2]	
CD40	HIGM3 (OMIM 606843)	AR	Clinically indistinguishable w/recurrent bacterial infections & opportunistic infections w/*P jirovecii*, *Cryptosporidium*, & sclerosing cholangitis [4]	Clinically indistinguishable [4]
UNG	HIGM5 (OMIM 608106)	AR	Recurrent bacterial infections	HIGM5 resembles HIGM2 in the ↑ in lymphoid hyperplasia compared to HIGM1. [2]
MSH6	Constitutional mismatch repair deficiency (See Lynch Syndrome.)	AR	↑ or normal IgM, ↓ or normal IgG, normal B cell counts, & normal memory B cells w/↓ class-switched B cells	• No recurrent infections • ↑ risk for cancers incl colorectal cancer, hereditary nonpolyposis colon cancer, & endometrial cancer
PMS2	Constitutional mismatch repair deficiency (See Lynch Syndrome.)	AR	• Recurrent infections • ↑ or normal IgM w/↓ IgG & IgA • Normal B cell counts but ↓ memory B cells	• Café au lait spots • Colorectal adenocarcinoma

Table 2. continued from previous page.

Gene(s)	Differential Disorder	MOI	Clinical Features of Differential Disorder	
			Overlapping w/HIGM1	Distinguishing from HIGM1
CD19 *CD81* *CR2* *ICOS* *IKZF1* *IL21* *IRF2BP2* *LRBA* *MS4A1* *NFKB1* *NFKB2* *TNFRSF13B* *TNFRSF13C*	Common variable immunodeficiency (CVID) (OMIM PS607594)	AR AD	• Recurrent sinopulmonary infections • ↓ immunoglobulins incl IgG & IgA • CD40LG protein may be ↓.	• No *CD40LG* pathogenic variant • May be assoc w/↓ number of total T cells or ↓ T-cell function [5]
ADA *AK2* *CD3D* *CD3E* *CD247* *CORO1A* *DCLRE1C* *IL2RG* *IL7R* *JAK3* *PRKDC* *PTPRC* *RAG1* *RAG2* [6]	Severe combined immunodeficiency (SCID) (See X-Linked SCID & Adenosine Deaminase Deficiency.)	AR XL	All SCIDs must be considered in infants presenting w/*P jirovecii* pneumonia.	• Most forms of SCID present w/absent T-cell function, quantitative abnormalities of T lymphocyte populations, & markedly ↓ mitogen function. • Hypomorphic *RAG2* variants reported in a male w/clinical & immunologic studies suggestive of HIGM [7]
AGMX2 *BLNK* *BTK* *CD79A* *CD79B* *IGHM* *IGLL1* *LRRC8A* *PIK3R1* *TCF3* *SLC39A7* [8]	Agammaglobulinemia (See X-Linked Agammaglobulinemia [XLA].)	AR AD XL	• Males w/agammaglobulinemia should be considered in differential of HIGM1. • XLA typically presents in 1st yr of life w/recurrent bacterial infections	Most individuals w/ agammaglobulinemia lack circulating B cells.
IKBKG (*NEMO*)	Ectodermal dysplasia & immunodeficiency 1 (OMIM 300291)	XL	• Serious infections, incl opportunistic infections, are a common complication at any age. • Variable immunoglobulins from agammaglobulinemia to normal or ↑ IgM, ↓ IgG, & low/↑ IgA w/↓ memory B cells	• *IKBKG*-related hyper IgM syndrome is generally assoc w/hypohydrotic ectodermal dysplasia. [9] • Invasive disease by MRSA & MSSA; osteopetrosis, lymphedema; conical shaped teeth
PIK3CD	Activated PI3 kinase-δ syndrome (OMIM 615513]	AD	• Recurrent infections w/*S pneumoniae* or *H influenzae* • Chronic lung disease • ↑ IgM, ↓/normal IgG/IgA • ↓ class-switched memory B cells	• Lymphoid hyperplasia • Lymphopenia, ↓ T/B cell counts • Severe response to herpes family virus (EBV, CMV, HSV, VZV)

Table 2. continued from previous page.

Gene(s)	Differential Disorder	MOI	Clinical Features of Differential Disorder	
			Overlapping w/HIGM1	Distinguishing from HIGM1
ATM	Ataxia-telangiectasia	AR	• Recurrent URTI/LRTI, malignancy • Normal/↑ IgM, normal to ↓ IgG/IgA, normal to ↓ T/B cells	• Ataxia, telangiectasias, hypotonia, dysarthria, radiosensitivity • Lymphopenia, ↑ α-fetoprotein, variable mitogen & antigen response
NBN	Nijmegen breakage syndrome	AR	• Recurrent URTI/LRTI, malignancy, autoimmune conditions (primarily hemolytic anemia) • Variable immunoglobulins w/ agammaglobulinemia to ↓ IgG/IgA & normal/↑ IgM	Microcephaly, facial features, short stature, café au lait spots, vitiligo, radiosensitivity
INO80	INO80 deficiency [10] (OMIM 610169)		• Recurrent bacterial infections • COPD • ↓ IgG & IgA • ↓ class-switched memory B cells	Normal CD40LG protein expression & no CD40LG pathogenic variant

AD = autosomal dominant; AR = autosomal recessive; COPD = chronic obstructive pulmonary disease; GI = gastrointestinal; *H* = *Haemophilus*; HIGM = hyper IgM syndrome; LRTI = lower respiratory tract infection; MOI = mode of inheritance; *P* = *Pneumocystis*; *S* = *Streptococcus*; URTI = upper respiratory tract infection; XL = X-linked

1. Minegishi et al [2000], Revy et al [2000], Lee et al [2005]

2. Imai et al [2003]

3. An autosomal dominant form of hyper IgM syndrome has been reported in four unrelated families with an identical pathogenic nonsense variant (p.Arg190Ter) in AICDA (reference sequence NM_020661.2) [Durandy et al 2005].

4. Ferrari et al [2001]

5. See Park et al [2011], Yong et al [2011], and Abbott & Gelfand [2015] for current reviews of CVID.

6. Note: A growing list of rare causes of SCID-like phenotypes include pathogenic variants in the following additional genes: *CD3G*, *CD8A*, *CHD7*, *CIITA*, *DOCK8*, *FOXN1*, *LCK*, *LIG4*, *MTHFD1*, *NHEJ1*, *ORAI1*, *PGM3*, *PNP*, *PRKDC*, *RFXANK* (*RFX-B*), *RFX5*, *RFXAP*, *RMRP*, *SLC46A1*, *STIM1*, *TBX1*, *TTC7A*, *ZAP70*.

7. Chou et al [2012]

8. Anzilotti et al [2019]

9. Jain et al [2001]

10. Kracker et al [2015]

The differential diagnosis of HIGM1 also includes the following disorders:

- **HIV infection.** Infection with HIV should be considered in any infant presenting with *Pneumocystis jirovecii* pneumonia.
- **Transient hypogammaglobulinemia of infancy.** Transient hypogammaglobulinemia of infancy is characterized by normal antibody production, normal growth patterns, and lack of opportunistic infections. Neonates and young infants may have diminished CD40L expression that improves with time [Nonoyama et al 1995].

Management

Evaluations Following Initial Diagnosis

To establish the extent of disease and needs in an individual diagnosed with X-linked hyper IgM syndrome, the evaluations summarized in Table 3 (if not performed as part of the evaluation that led to the diagnosis) are recommended.

Table 3. Recommended Evaluations Following Initial Diagnosis in Individuals with X-Linked Hyper IgM Syndrome

System/Concern	Evaluation	Comment
Hematology/ Immunology	• CBC w/differential • IgG levels • T, B, & NK cell numbers	For evidence of cytopenias
Pulmonary	Baseline chest radiograph & pulmonary function testing	For chronic lung changes due to infection; if present, consider pulmonology evaluation.
Gastrointestinal	PCR-based testing of stools	For presence of *Cryptosporodium* or other enteric pathogens; if present, partner w/gastroenterologist.
	Nutritional assessment	
Hepatobiliary	Baseline liver function testing & liver / biliary tree ultrasound	For evidence of hepatocyte dysfunction & developing biliary dilatation
Transplantation	All individuals should be offered HLA typing at diagnosis.	For consideration of HSCT
Other	Consultation w/clinical geneticist &/or genetic counselor	

CBC = complete blood count; HLA = human leukocyte antigen; HSCT = hematopoietic stem cell transplant; PCR = polymerase chain reaction

Treatment of Manifestations

For a concise summary of current clinical management practices in this disorder, see Davies & Thrasher [2010] and de la Morena et al [2017].

Hematopoietic stem cell transplant (HSCT). Currently HSCT is the only curative therapy available for HIGM1. Best outcomes are reported for those individuals transplanted before age ten years and without evidence of end organ damage, especially liver disease [de la Morena et al 2017, Ferrua et al 2019]. Myeloablative conditioning regimens result in better survival; mismatched-related-donor and matched-unrelated-donor transplants were associated with increased morbidity compared to matched sib donors. Approximately 15% of individuals may reject the graft (mainly after matched unrelated transplant and reduced intensity conditioning) and require a second or third transplant. In one series, among 130 transplanted individuals with HIGM1, a third required ongoing immunoglobulin replacement five years after transplantation [Ferrua et al 2019].

Note: Liver transplantation has been performed successfully for end-stage liver disease but for best outcome requires that HSCT be performed following the liver allograft [Bucciol et al 2019].

Table 4. Treatment of Manifestations in Individuals with X-Linked Hyper IgM Syndrome

Manifestation/ Concern	Treatment	Considerations/Other
Recurrent infections	• Immunoglobulin replacement w/intravenous or subcutaneous immunoglobulin starting at diagnosis Initial dosing for IgG replacement: 0.4-0.6 g/kg every 3-4 wks for IV, or ≥100 mg/kg dose weekly for subcutaneous Ig. Titrate IgG levels as for primary antibody deficiency syndromes. • Prophylactic antibiotics against opportunistic infections incl *P jirovecii*	Discussion re prophylactic use of azithromycin or nitazoxanide for all affected individuals for prevention of *Crypstosporidium* is ongoing. While not standard of care, it should be considered for those living in / traveling to an area w/↑ *Cryptosporidium* rates.

Table 4. continued from previous page.

Manifestation/ Concern	Treatment	Considerations/Other
	• Institute appropriate antimicrobial therapy for acute infections. • Aggressively evaluate pulmonary infections (incl use of diagnostic bronchoalveolar lavage) to define specific etiology. • Prevention of infections [1]	
Immunodeficiency	Only current curative treatment is HSCT, preferably at age <10 yrs.	Modified conditioning regimens may be needed in those w/preexisting liver disease, & hepatic transplant along w/ HSCT may be required.
Chronic neutropenia	Recombinant GCSF	
Malnutrition & poor growth	Total parenteral nutrition & consultation w/clinical dietary nutritionist may be required to optimize caloric intake.	
Sclerosing cholangitis	Some males w/end-stage sclerosing cholangitis have been treated successfully w/orthotopic liver transplantation closely assoc w/allogeneic bone marrow transplantation. Infectious etiologies need to be pursued & treated prior to transplantation.	
Autoimmune disorders	Treatment of autoimmune disorders usually involves judicious use of immunosuppressants tailored to individual's diagnosis.	
Cancer	Treatment should follow standard protocols/therapies for individual cancers in conjunction w/ immunologist.	

GCSF = granulocyte colony-stimulating factor; HSCT = hematopoietic stem-cell transplantation; *P* = *Pneumocystis*

1. The following methods are used to prevent infection:

Antibiotic prophylaxis. Prophylaxis for pneumonia secondary to *Pneumocystis jirovecii* (PJP) is indicated for all children with HIGM1 due to the high risk of developing PJP during the first two years of life. There is no standard-of-care approach established for length of PJP prophylaxis. However, individuals with HIGM1 who develop PJP after age two years should continue prophylaxis for life or until after HSCT transplant when normal immune function is established. Typical prophylaxis is trimethoprim-sulfamethoxazole orally, pentamidine by intravenous or inhalation therapy, dapsone, and atovaquone.

Immunoglobulin (either subcutaneous or intravenous). Immunoglobulin replacement should be considered at the time of diagnosis, as individuals with HIGM1 cannot generate antibodies to encapsulated bacteria naturally and are at risk for overwhelming infection from these organisms. IgG replacement is a highly purified blood derivative (a combination of many specific antimicrobial antibodies) that is typically given every three to four weeks or can be given subcutaneously, usually on a weekly basis.

Additional antibiotic prophylaxis should be evaluated on a case-by-case basis with ongoing questions regarding *Cryptosporidum* prophylaxis not yet being standardized.

Routine childhood immunizations (killed vaccines) may be safely administered but do not preclude the need for immunoglobulin replacement. Live vaccines (e.g., rotavirus, MMR, varicella, live attenuated polio, and BCG) should not be given to individuals with HIGM1.

Only boiled and/or filtered water should be ingested. Avoid swimming in non-chlorinated pools. Avoid swimming in lakes and ponds. Children should avoid water parks and farm animals.

Surveillance

No guidelines have been published for ongoing surveillance in individuals with HIGM1. Table 5 presents the current recommendations of the authors.

Table 5. Recommended Surveillance for Individuals with X-Linked Hyper IgM Syndrome

System/Concern	Evaluation	Frequency
Hematology	CBC w/differential to monitor for cytopenias	At least every 6 mos to yrly if stable or w/any change in clinical status
Immunology	IgG levels	• IgG frequency depends on time needed to achieve adequate IgG levels; similar to those w/primary antibody deficiency syndromes. • Adults: at least yrly
	Lymphocyte subpopulations: T, B, & NK cell numbers	Given progressive T, B, & NK loss over time, consider obtaining yrly in nontransplanted adolescents & adults.
	CD40L expression in transplanted individuals	Monitor CD40L expression in activated T-cells at least yrly in those who have had HSCT, or if any change in clinical status.
Pulmonary	Pulmonary function tests	Yrly for those age >7 yrs or if change in clinical status
	Chest radiograph w/follow up of pulmonary infiltrates w/high-resolution CT scan	As clinically indicated
Gastrointestinal	PCR-based testing of stools for infectious etiologies	At least every 6 mos or if diarrhea present or exposure occurs
	Liver function tests	• Children: at least every 4-6 mos or if change in clinical status • Adults: at least 1-2x/yr or if change in clinical status
	Liver ultrasound	≥1x/yr or if change in clinical status
	• Monitor growth in children. • Measure weight in adolescents & adults at least 2x/yr	• Children: at every visit; at least every 4-6 mos • Adolescents/adults: at least 2x/yr • If any change in clinical status
Oncology	Physical exam	• Children: at least every 4-6 mos • Adolescents/adults: at least 1-2x/yr • Low threshold for lymph node biopsy

CBC = complete blood count; PCR = polymerase chain reaction

Agents/Circumstances to Avoid

Avoid areas that place the individual at risk of contracting *Cryptosporidium* including pools, lakes, ponds, or certain water sources. Avoid drinking unpurified or unfiltered water.

Live vaccines (e.g., rotavirus, MMR, varicella, live attenuated polio, and BCG) should not be given to individuals with HIGM1.

Evaluation of Relatives at Risk

It is appropriate to clarify the genetic status of newborn at-risk relatives of an affected individual in order to identify as early as possible those who would benefit from early diagnosis and prompt initiation of treatment and prevention of infections.

See Genetic Counseling for issues related to testing of at-risk relatives for genetic counseling purposes.

Therapies Under Investigation

Research into autologous gene corrective therapy is ongoing [Hubbard et al 2016, Kuo et al 2018].

Search ClinicalTrials.gov in the US and EU Clinical Trials Register in Europe for access to information on clinical studies for a wide range of diseases and conditions.

Genetic Counseling

Genetic counseling is the process of providing individuals and families with information on the nature, mode(s) of inheritance, and implications of genetic disorders to help them make informed medical and personal decisions. The following section deals with genetic risk assessment and the use of family history and genetic testing to clarify genetic status for family members; it is not meant to address all personal, cultural, or ethical issues that may arise or to substitute for consultation with a genetics professional. —ED.

Mode of Inheritance

X-linked hyper IgM syndrome (HIGM1) is inherited in an X-linked manner.

Risk to Family Members

Parents of a male proband

- The father of an affected male will not have HIGM1 nor will he be hemizygous for the *CD40LG* pathogenic variant; therefore, he does not require further evaluation/testing.
- In a family with more than one affected individual, the mother of an affected male is an obligate heterozygote. Note: If a woman has more than one affected child and no other affected relatives and if the *CD40LG* pathogenic variant cannot be detected in her leukocyte DNA, she most likely has germline mosaicism.
- If a male is the only affected family member (i.e., a simplex case), the mother may be a heterozygote or the affected male may have a *de novo* pathogenic variant, in which case the mother is not a heterozygote.

  De novo pathogenic variants occur in approximately one third of simplex cases. Therefore, the mother of an affected male who has no family history of HIGM1 has a 2/3 chance of being heterozygous for the *CD40LG* pathogenic variant.

Sibs of a male proband. The risk to sibs depends on the genetic status of the mother:

- If the mother is heterozygous for the *CD40LG* pathogenic variant, the chance of transmitting the pathogenic variant in each pregnancy is 50%. Male sibs who inherit the variant will be affected; female sibs who inherit the variant are typically asymptomatic but may have a range of clinical manifestations depending on X-chromosome inactivation (see Clinical Description, Heterozygous Females).
- If the proband represents a simplex case and if the *CD40LG* pathogenic variant cannot be detected in the leukocyte DNA of the mother, the sibs remain at increased risk because of the theoretic possibility of maternal germline mosaicism.

Offspring of a male proband. Affected males transmit the *CD40LG* pathogenic variant to:

- All of their daughters, who will typically be asymptomatic but may have a range of clinical manifestations depending on X-chromosome inactivation (see Clinical Description, Heterozygous Females);
- None of their sons.

Other family members

- A male proband's maternal aunts or other maternal relatives and their offspring may be at risk of being heterozygous for a *CD40LG* pathogenic variant (if female) or of being affected with a *CD40LG*-related disorder (if male). The precise risk to the proband's maternal relatives depends on the family relationships.
- Note: Molecular genetic testing may be able to identify the family member in whom a *de novo* pathogenic variant arose, information that could help determine genetic risk status of the extended family.

Heterozygote Detection

Molecular genetic testing of at-risk female relatives to determine their genetic status is most informative if the pathogenic variant has been identified in an affected male relative.

If an affected male is not available for testing, perform molecular genetic testing first by sequence analysis, and if no pathogenic variant is identified, by gene-targeted deletion/duplication analysis.

Note: CD40L expression by flow cytometry may be helpful but is not a diagnostic test for the detection of heterozygotes.

Related Genetic Counseling Issues

See Management, Evaluation of Relatives at Risk for information on evaluating at-risk relatives for the purpose of early diagnosis and treatment.

Family planning

- The optimal time for determination of genetic risk, clarification of genetic status, and discussion of the availability of prenatal/preimplantation genetic testing is before pregnancy.
- It is appropriate to offer genetic counseling (including discussion of potential risks to offspring and reproductive options) to young adults who are affected, are heterozygous, or are at risk of being heterozygous.

DNA banking. Because it is likely that testing methodology and our understanding of genes, pathogenic mechanisms, and diseases will improve in the future, consideration should be given to banking DNA from probands in whom a molecular diagnosis has not been confirmed (i.e., the causative pathogenic mechanism is unknown). For more information, see Huang et al [2022].

Prenatal Testing and Preimplantation Genetic Testing

Once the *CD40LG* pathogenic variant has been identified in an affected family member, prenatal and preimplantation genetic testing for HIGM1 are possible.

Differences in perspective may exist among medical professionals and within families regarding the use of prenatal testing, particularly if the testing is being considered for the purpose of pregnancy termination rather than early diagnosis. While most centers would consider use of prenatal testing to be a personal decision, discussion of these issues may be helpful.

Resources

GeneReviews staff has selected the following disease-specific and/or umbrella support organizations and/or registries for the benefit of individuals with this disorder and their families. GeneReviews is not responsible for the information provided by other organizations. For information on selection criteria, click here.

- **Hyper IgM Foundation**
  215 West 101st Street

Suite 7B
New York NY 10025
Phone: 646-883-4446
Email: info@hyperigm.org
www.hyperigm.org

- **Immune Deficiency Foundation**
  Phone: 800-296-4433
  Fax: 410-321-9165
  Email: idf@primaryimmune.org
  primaryimmune.org
- **ImmUnity Canada**
  Canada
  Phone: 250-381-7134; 877 -607-2476
  Email: info@immunitycanada.org
  immunitycanada.org
- **Jeffrey Modell Foundation/National Primary Immunodeficiency Resource Center**
  Email: info@jmfworld.org
  info4pi.org
- **European Society for Immunodeficiencies (ESID) Registry**
  Email: esid-registry@uniklinik-freiburg.de
  ESID Registry
- **United States Immunodeficiency Network (USIDNET) Registry**
  Email: contact@usidnet.org
  Enrolling Institutions

Molecular Genetics

Information in the Molecular Genetics and OMIM tables may differ from that elsewhere in the GeneReview: tables may contain more recent information. —ED.

Table A. X-Linked Hyper IgM Syndrome: Genes and Databases

Gene	Chromosome Locus	Protein	Locus-Specific Databases	HGMD	ClinVar
CD40LG	Xq26.3	CD40 ligand	CD40LG @ LOVD CCHMC - Human Genetics Mutation Database (CD40LG) CD40Lbase: Mutation registry for X-linked Hyper-IgM syndrome (CD40LG)	CD40LG	CD40LG

Data are compiled from the following standard references: gene from HGNC; chromosome locus from OMIM; protein from UniProt. For a description of databases (Locus Specific, HGMD, ClinVar) to which links are provided, click here.

Table B. OMIM Entries for X-Linked Hyper IgM Syndrome (View All in OMIM)

300386	CD40 LIGAND; CD40LG
308230	IMMUNODEFICIENCY WITH HYPER-IgM, TYPE 1; HIGM1

Molecular Pathogenesis

CD40LG encodes CD40 ligand (CD40L) which is a small, 261-amino-acid transmembrane protein. The protein has three functional domains: an intracytoplasmic domain, a transmembrane domain, and an extracellular domain that shares considerable sequence homology to tumor necrosis factor alpha. CD40L, expressed primarily on CD4+ T cells, binds to CD40 on the surface of B cells to promote immunoglobulin isotype switching in B lymphocytes. CD40L also plays an important role in T-cell function, particularly in the interaction with monocyte-derived antigen-presenting cells [Jain et al 1999].

Pathogenic variants in *CD40LG* lead to changes in the amino acid sequence, abnormal splicing of the protein, premature truncation of the protein, or complete absence of CD40 ligand protein. Persons with pathogenic variants in *CD40LG* are unable to make high-affinity functional antibodies and cytokines, resulting in a high incidence of opportunistic infections.

Mechanism of disease causation. The HIGM1 syndrome is caused by loss of function as evidenced by multiple partial- or whole-gene deletion and gross-insertion pathogenic variants of *CD40LG*. Missense pathogenic variants may affect core packaging, prevent binding to CD40L, or affect trimer formation [Seyama et al 1998].

***CD40LG*-specific laboratory technical considerations.** The presence of CD40L based on flow cytometry alone does not rule out a diagnosis of HIGM1 [Lee et al 2005].

Flow cytometry using anti-CD40L monoclonal antibodies can confirm the diagnosis of HIGM1 in some affected individuals:

- Those who produce no CD40L protein on the surface of CD4+ cells due to missense or frameshift variants
- Those who produce an altered protein structure of CD40L, preventing anti-CD40L antibody binding

Anti-CD40L antibody testing will not identify affected individuals with pathogenic variants in the intracellular tail or those producing reduced amounts of normal CD40L.

Table 6. Notable *CD40LG* Pathogenic Variants

Reference Sequences	DNA Nucleotide Change	Predicted Protein Change	Comment [Reference]
NM_000074.2 NP_000065.1	c.31C>T	p.Arg11Ter	Assoc w/milder clinical phenotype [Seyama et al 1998, Lee et al 2005]
	c.761C>T	p.Thr254Met	

Variants listed in the table have been provided by the authors. *GeneReviews* staff have not independently verified the classification of variants.
GeneReviews follows the standard naming conventions of the Human Genome Variation Society (varnomen.hgvs.org). See Quick Reference for an explanation of nomenclature.

Chapter Notes

Author History

M Teresa de la Morena, MD (2020-present)
Clinton P Dunn, MD (2020-present)
Alexandra H Filipovich, MD; Cincinnati Children's Hospital Medical Center (2007-2020)
Judith Johnson, MS; Cincinnati Children's Hospital Medical Center (2007-2020)
Kejian Zhang, MD, MBA; Cincinnati Children's Hospital Medical Center (2007-2020)

Revision History

- 20 February 2020 (ha) Comprehensive update posted live

- 24 January 2013 (cd) Revision: deletion/duplication analysis available clinically
- 21 June 2012 (me) Comprehensive update posted live
- 2 February 2010 (me) Comprehensive update posted live
- 31 May 2007 (me) Review posted live
- 20 February 2007 (jj) Original submission

References

Literature Cited

Abbott JK, Gelfand EW. Common variable immunodeficiency: diagnosis, management, and treatment. Immunol Allergy Clin North Am. 2015;35:637–58. PubMed PMID: 26454311.

Agematsu K, Nagumo H, Shinozaki K, Hokibara S, Yasui K, Terada K, Kawamura N, Toba T, Nonoyama S, Ochs HD, Komiyama A. Absence of IgD-CD27 (+) memory B cell population in X-linked hyper-IgM Syndrome. J Clin Invest. 1998;102:853–60. PubMed PMID: 9710455.

Anzilotti C, Swan DJ, Boisson B, Deobagkar-Lele M, Oliveira C, Chabosseau P, Engelhardt KR, Xu X, Chen R, Alvarez L, Berlinguer-Palmini R, Bull KR, Cawthorne E, Cribbs AP, Crockford TL, Dang TS, Fearn A, Fenech EJ, de Jong SJ, Lagerholm BC, Ma CS, Sims D, van den Berg B, Xu Y, Cant AJ, Kleiner G, Leahy TR, de la Morena MT, Puck JM, Shapiro RS, van der Burg M, Chapman JR, Christianson JC, Davies B, McGrath JA, Przyborski S, Santibanez Koref M, Tangye SG, Werner A, Rutter GA, Padilla-Parra S, Casanova JL, Cornall RJ, Conley ME, Hambleton S. An essential role for the Zn2+ transporter ZIP7 in B cell development. Nat Immunol. 2019;20:350–61. PubMed PMID: 30718914.

Bucciol G, Nicholas SK, Calvo PL, Cant A, Edgar JDM, Espanol T, Ferrua F, Galicchio M, Gennery AR, Hadzic N, Hanson I E, Kusminsky G, Lange A, Lanternier F, Mahlaoui N, Moshous D, Nademi Z, Neven B, Oleastro M, Porta F, Quarello P, Silva M, Slatter MA, Soncini E, Stefanowicz M, Tandoi F, Teisseyre M, Torgerson TR, Veys P, Weinacht KG, Wolska-Kuśnierz B, Pirenne J, de la Morena MT, Meyts I. Combined liver and hematopoietic stem cell transplantation in patients with X-linked hyper-IgM syndrome. J Allergy Clin Immunol. 2019;143:1952–6.e6. PubMed PMID: 30682461.

Cabral-Marques O, Klaver S, Schimke LF, Ascendino ÉH, Khan TA, Pereira PV, Falcai A, Vargas-Hernández A, Santos-Argumedo L, Bezrodnik L, Moreira I, Seminario G, Di Giovanni D, Raccio AG, Porras O, Weber CW, Ferreira JF, Tavares FS, de Carvalho E, Valente CF, Kuntze G, Galicchio M, King A, Rosário-Filho NA, Grota MB, dos Santos Vilela MM, Di Gesu RS, Lima S, de Souza Moura L, Talesnik E, Mansour E, Roxo-Junior P, Aldave JC, Goudouris E, Pinto-Mariz F, Berrón-Ruiz L, Staines-Boone T, Calderón WO, del Carmen Zarate-Hernández M, Grumach AS, Sorensen R, Durandy A, Torgerson TR, Carvalho BT, Espinosa-Rosales F, Ochs HD, Condino-Neto A. First report of the Hyper IgM Syndrome Registry of the Latin American Society for Immunodeficiencies: novel mutations, unique infections, and outcomes. J Clin Immunol. 2014;34:146–56. PubMed PMID: 24402618.

Cabral-Marques O, França TT, Al-Sbiei A, Schimke LF, Khan TA, Feriotti C, da Costa TA, Junior OR, Weber CW, Ferreira JF, Tavares FS, Valente C, Di Gesu RSW, Iqbal A, Riemekasten G, Amarante-Mendes GP, Marzagão Barbuto JA, Costa-Carvalho BT, Pereira PVS, Fernandez-Cabezudo MJ, Calich VLG, Notarangelo LD, Torgerson TR, Al-Ramadi BK, Ochs HD, Condino-Neto A. CD40 ligand deficiency causes functional defects of peripheral neutrophils that are improved by exogenous IFN-γ. J Allergy Clin Immunol. 2018;142:1571–88.e9. PubMed PMID: 29518426.

Chou J, Hanna-Wakim R, Tirosh I, Kane J, Fraulino D, Lee Y N, Ghanem S, Mahfouz I, Megarbane A, Lefranc G, Inati A, Dbaibo G, Giliani S, Notarangelo LD, Geha R S, Massaad MJ. A novel homozygous mutation in recombination activating gene 2 in two relatives with different clinical phenotypes: Omenn syndrome and hyper-IgM syndrome. J Allergy Clin Immunol. 2012;130:1414–6. PubMed PMID: 22841008.

Davies EG, Thrasher AJ. Update on the hyper immunoglobulin M syndromes. Br J Haematol. 2010;149:167–80. PubMed PMID: 20180797.

de la Morena MT. Clinical phenotypes of hyper IgM syndromes. J Allergy Clin Immunol Pract. 2016;4:1023–36. PubMed PMID: 27836054.

de la Morena MT, Leonard D, Torgerson TR, Cabral-Marques O, Slatter M, Aghamohammadi A, Chandra S, Murguia-Favela L, Bonilla FA, Kanariou M, Damrongwatanasuk R, Kuo CY, Dvorak CC, Meyts I, Chen K, Kobrynski L, Kapoor N, Richter D, DiGiovanni D, Dhalla F, Farmaki E, Speckmann C, Español T, Shcherbina A, Hanson IC, Litzman J, Routes JM, Wong M, Fuleihan R, Seneviratne SL, Small TN, Janda A, Bezrodnik L, Seger R, Raccio AG, Edgar JD, Chou J, Abbott JK, van Montfrans J, González-Granado LI, Bunin N, Kutukculer N, Gray P, Seminario G, Pasic S, Aquino V, Wysocki C, Abolhassani H, Dorsey M, Cunningham-Rundles C, Knutsen AP, Sleasman J, Costa Carvalho BT, Condino-Neto A, Grunebaum E, Chapel H, Ochs HD, Filipovich A, Cowan M, Gennery A, Cant A, Notarangelo LD, Roifman CM. Long-term outcomes of 176 patients with X-linked hyper-IgM syndrome treated with or without hematopoietic cell transplantation. J Allergy Clin Immunol. 2017;139:1282–92. PubMed PMID: 27697500.

de Saint Basile G, Tabone MD, Durandy A, Phan F, Fischer A, Le Deist F. CD40 ligand expression deficiency in a female carrier of the X-linked hyper-IgM syndrome as a result of X chromosome lyonization. Eur J Immunol. 1999;29:367–73. PubMed PMID: 9933119.

Durandy A, Revy P, Imai K, Fischer A. Hyper-immunoglobulin M syndromes caused by intrinsic B-lymphocyte defects. Immunol Rev. 2005;203:67–79. PubMed PMID: 15661022.

Erdos M, Garami M, Rákóczi E, Zalatnai A, Steinbach D, Baumann U, Kropshofer G, Tóth B, Maródi L. Neuroendocrine carcinoma associated with X-linked hyper-immunoglobulin M syndrome: report of four cases and review of the literature. Clin Immunol. 2008;129:455–61. PubMed PMID: 18805740.

Ferrari S, Giliani S, Insalaco A, Al-Ghonaium A, Soresina AR, Loubser M, Avanzini MA, Marconi M, Badolato R, Ugazio AG, Levy Y, Catalan N, Durandy A, Tbakhi A, Notarangelo LD, Plebani A. Mutations of CD40 gene cause an autosomal recessive form of immunodeficiency with hyper IgM. Proc Natl Acad Sci U S A. 2001;98:12614–9. PubMed PMID: 11675497.

Ferrua F, Galimberti S, Courteille V, Slatter MA, Booth C, Moshous D, Neven B, Blanche S, Cavazzana A, Laberko A, Shcherbina A, Balashov D, Soncini E, Porta F, Al-Mousa H, Al-Saud B, Al-Dhekri H, Arnaout R, Formankova R, Bertrand Y, Lange A, Smart J, Wolska-Kusnierz B, Aquino VM, Dvorak CC, Fasth A, Fouyssac F, Heilmann C, Hoenig M, Schuetz C, Kelečić J, Bredius RGM, Lankester AC, Lindemans CA, Suarez F, Sullivan KE, Albert MH, Kałwak K, Barlogis V, Bhatia M, Bordon V, Czogala W, Alonso L, Dogu F, Gozdzik J, Ikinciogullari A, Kriván G, Ljungman P, Meyts I, Mustillo P, Smith AR, Speckmann C, Sundin M, Keogh SJ, Shaw PJ, Boelens JJ, Schulz AS, Sedlacek P, Veys P, Mahlaoui N, Janda A, Davies EG, Fischer A, Cowan MJ, Gennery AR, et al. Hematopoietic stem cell transplantation for CD40 Ligand deficiency: Results from an EBMT/ESID-IEWP-SCETIDE-PIDTC study. J Allergy Clin Immunol. 2019;143:2238–53. PubMed PMID: 30660643.

Filipovich L, Gross T. Immunodeficiency and cancer. In: Abeloff M, Armitage J, Niederhuber J, Kastan M, McKenna WG, eds. *Clinical Oncology*. 3 ed. London, UK: Elsevier/Churchill Livingstone; 2004:287-98.

Gallerani I, Innocenti DD, Coronella G, Berti S, Amato L, Moretti S, Fabbri P. Cutaneous sarcoid-like granulomas in a patient with X-linked hyper-IgM syndrome. Pediatr Dermatol. 2004;21:39–43. PubMed PMID: 14871324.

Gilmour KC, Walshe D, Heath S, Monaghan G, Loughlin S, Lester T, Norbury G, Cale CM. Immunological and genetic analysis of 65 patients with a clinical suspicion of X linked hyper-IgM. Mol Pathol. 2003;56:256–62. PubMed PMID: 14514918.

Hayward AR, Levy J, Facchetti F, Notarangelo L, Ochs HD, Etzioni A, Bonnefoy JY, Cosyns M, Weinberg A. Cholangiopathy and tumors of the pancreas, liver, and biliary tree in boys with X-linked immunodeficiency with hyper-IgM. J Immunol. 1997;158:977–83. PubMed PMID: 8993019.

Ho HE, Byun M, Cunningham-Rundles C. Disseminated cutaneous warts in X-linked hyper IgM syndrome. J Clin Immunol. 2018;38:454–6. PubMed PMID: 29730845.

Hollenbaugh D, Wu LH, Ochs HD, Nonoyama S, Grosmaire LS, Ledbetter JA, Noelle RJ, Hill H, Aruffo A. The Random Inactivation of the X Chromosome Carrying the Defective Gene Responsible for X-linked Hyper IgM Syndrome (X-HIM) in Female Carriers of HIGM1. J Clin Invest. 1994;94:616–22. PubMed PMID: 7518839.

Huang SJ, Amendola LM, Sternen DL. Variation among DNA banking consent forms: points for clinicians to bank on. J Community Genet. 2022;13:389–97. PubMed PMID: 35834113.

Hubbard N, Hagin D, Sommer K, Song Y, Khan I, Clough C, Ochs H D, Rawlings D J, Scharenberg A M, Torgerson TR. Targeted gene editing restores regulated CD40L function in X-linked hyper-IgM syndrome. Blood. 2016;127:2513–22. PubMed PMID: 26903548.

Imai K, Catalan N, Plebani A, Maródi L, Sanal O, Kumaki S, Nagendran V, Wood P. Hyper-IgM syndrome type 4 with a B lymphocyte-intrinsic selective deficiency in Ig class switch recombination. J Clin Invest. 2003;112:136–42. PubMed PMID: 12840068.

Jain A, Atkinson TP, Lipsky PE, Slater JE, Nelson DL, Strober W. Defects of T-cell effector function and post-thymic maturation in X-linked hyper-IgM syndrome. J Clin Invest. 1999;103:1151–8. PubMed PMID: 10207167.

Jain A, Ma CA, Liu S, Brown M, Cohen J, Strober W. Specific missense mutations in NEMO result in hyper-IgM syndrome with hypohydrotic ectodermal dysplasia. Nat Immunol. 2001;2:223–8. PubMed PMID: 11224521.

Kracker S, Di Virgilio M, Schwartzentruber J, Cuenin C, Forveille M, Deau MC, McBride KM, Majewski J, Gazumyan A, Seneviratne S, Grimbacher B, Kutukculer N, Herceg Z, Cavazzana M, Jabado N, Nussenzweig MC, Fischer A, Durandy A. An Inherited immunoglobulin class-switch recombination deficiency associated with a defect in the INO80 Chromatin Remodeling Complex. J Allergy Clin Immunol. 2015; 2015;135:998–1007.e6. PubMed PMID: 25312759.

Kuo C Y, Long J D, Campo-Fernandex B, de Oliveira S, Cooper AR, Romero Z, Hoban MD, Joglekar AV, Lill GR, Kaufman ML, Fitz-Gibbon S, Wang X, Hollis RP, Kohn DB. Site-specific gene editing of human hematopoietic stem cells for X-linked hyper-IgM syndrome. Cell Rep. 2018;23:2606–16. PubMed PMID: 29847792.

Le Coz C, Trofa M, Syrett CM, Martin A, Jyonouchi H, Jyonouchi S, Anguera MC, Romberg N. CD40LG duplication-associated autoimmune disease is silenced by nonrandom X-chromosome inactivation. J Allergy Clin Immunol. 2018;141:2308–11.e7. PubMed PMID: 29499223.

Lee WI, Torgerson TR, Schumacher MJ, Yel L, Zhu Q, Ochs HD. Molecular analysis of a large cohort of patients with the hyper immunoglobulin M (IgM) syndrome. Blood. 2005;105:1881–90. PubMed PMID: 15358621.

Leven EA, Maffucci P, Ochs H, Scholl PR, Buckley RB, Fuleihan RL, Geha RS, Cunningham CK, Bonilla FA, Conley ME, Ferdman RM, Hernandez-Trujilo V, Puck JM, Sullivan K, Secord EA, Ramesh M, Cunningham-Rundles C. Hyper IgM syndrome: a report from the USIDNET Registry. J Clin Immunol. 2016;36:490–501. PubMed PMID: 27189378.

Levy J, Espanol-Boren T, Thomas C, Fischer A, Tovo P, Bordigioni P, Resnick I, Fasth A, Baer M, Gomez L, Sanders EAM, Tabone MD, Plantaz D, Etzioni A, Monafo V, Abinun M, Hammarstrom L, Abrahamsen T, Jones A, Finn A, Klemola T, DeVries E, Sanal O, Peitsch MC, Notarangelo LD. Clinical spectrum of X-linked hyper IgM syndrome. J Pediatr. 1997;131:47–54. PubMed PMID: 9255191.

Lobo FM, Scholl PR, Fuleihan RL. CD40 ligand-deficient T cells from X-linked hyper-IgM syndrome carriers have intrinsic priming capability. J Immunol. 2002;168:1473–8. PubMed PMID: 11801691.

Lougaris V, Lanzi G, Manuela B, Gazzurelli L, Vairo D, Lorenzini T, Badolato R, Notarangelo LD, Boschi A, Moratto D, Plebani A. Progressive severe B cell and NK cell deficiency with T cell senescence in adult CD40L deficiency. Clin Immunol. 2018;190:11–14. PubMed PMID: 29476811.

Minegishi Y, Lavoie A, Cunningham-Rundles C, Bedard PM, Hebert J, Cote L, Dan K, Sedlak D, Buckley RH, Fischer A, Durandy A, Conley ME. Mutations in activation-induced cytidine deaminase in patients with hyper IgM syndrome. Clin Immunol. 2000;97:203–10. PubMed PMID: 11112359.

Nicolaides RE, de la Morena MT. Inherited and acquired clinical phenotypes associated with neuroendocrine tumors. Curr Opin Allergy Clin Immunol. 2017;17:431–42. PubMed PMID: 29040209.

Nonoyama S, Penix LA, Edwards CP, Lewis DB, Ito S, Aruffo A, Wilson CB, Ochs HD. Diminished Expression of CD40 ligand by activated neonatal T cells. J Clin Invest. 1995;95:66–75. PubMed PMID: 7814647.

Notarangelo LD, Hayward AR. X-linked immunodeficiency with hyper-IgM (XHIM). Clin Exp Immunol. 2000;120:399–405. PubMed PMID: 10844515.

Park JH, Resnick ES, Cunningham-Rundles C. Perspectives on common variable immune deficiency. Ann N Y Acad Sci. 2011;1246:41–9. PubMed PMID: 22236429.

Prasad ML, Velickovic M, Weston SA, Benson EM. Mutational screening of the CD40 ligand (CD40L) gene in patients with X linked hyper-IgM syndrome (XHIM) and determination of carrier status in female relatives. J Clin Pathol. 2005;58:90–2. PubMed PMID: 15623492.

Rawat A, Mathew B, Pandiarajan V, Jindal A, Sharma M, Suri D, Gupta A, Goel S, Karim A, Saikia B, Minz RW, Imai K, Nonoyama S, Ahara O, Giliani SC, Notarangelo LD, Chan KW, Lau YL, Singh S. Clinical and molecular features of X-linked hyper IgM syndrome - an experience from North India. Clin Immunol. 2018;195:59–66. PubMed PMID: 30053428.

Revy P, Muto T, Levy Y, Geissmann F, Plebani A, Sanal O, Catalan N, Forveille M, Dufourcq-Labelouse R, Gennery A, Tezcan I, Ersoy F, Kayserili H, Ugazio AG, Brousse N, Muramatsu M, Notarangelo LD, Kinoshita K, Honjo T, Fischer A, Durandy A. Activation-induced cytidine deaminase (AID) deficiency causes the autosomal recessive form of the hyper-IgM syndrome (HIGM2). Cell. 2000;102:565–75. PubMed PMID: 11007475.

Richards S, Aziz N, Bale S, Bick D, Das S, Gastier-Foster J, Grody WW, Hegde M, Lyon E, Spector E, Voelkerding K, Rehm HL, et al. Standards and guidelines for the interpretation of sequence variants: a joint consensus recommendation of the American College of Medical Genetics and Genomics and the Association for Molecular Pathology. Genet Med. 2015;17:405–24. PubMed PMID: 25741868.

Schuster A, Apfelstedt-Sylla E, Pusch CM, Zrenner E, Thirkill CE. Autoimmune retinopathy with RPE hypersensitivity and "negative ERG" in X-linked hyper-IgM syndrome. Ocul Immunol Inflamm. 2005;13:235–43. PubMed PMID: 16019685.

Seyama K, Nonoyama S, Gangsaas I, Hollenbaugh D, Pabst HF, Aruffo A, Ochs HD. Mutations of the CD40 ligand gene and its effect on CD40 ligand expression in patients with X-linked hyper IgM syndrome. Blood. 1998;92:2421–34. PubMed PMID: 9746782.

Tafakori Delbari M, Cheraghi T, Yazdani R, Fekrvand S, Delavari S, Azizi G, Chavoshzadeh Z, Mahdaviani SA, Ahanchian H, Khoshkhui M, Behmanesh F, Aleyasin S, Esmaeilzadeh H, Jabbari-Azad F, Fallahpour M, Zamani M, Madani SP, Moazzami B, Habibi S, Rezaei A, Lotfalikhani A, Movahed M, Shariat M, Kalantari A, Babaei D, Darabi M, Parvaneh N, Rezaei N, Abolhassani H, Aghamohammadi A. Clinical manifestations, immunological characteristics and genetic analysis of patients with hyper-immunoglobulin M syndrome in Iran. Int Arch Allergy Immunol. 2019;180:52–63. PubMed PMID: 31117086.

Wang LL, Zhou W, Zhao W, Tian Z, Wang W, Wang X, Chen T. Clinical features and genetic analysis of 20 Chinese patients with X-linked hyper-IgM syndrome. J Immunol Res. 2014;2014:683160. PubMed PMID: 25215306.

Winkelstein JA, Marino MC, Ochs H, Fuleihan R, Scholl PR, Geha R, Stiehm ER, Conley ME. The X-linked hyper-IgM syndrome: clinical and immunologic features of 79 patients. Medicine (Baltimore). 2003;82:373–84. PubMed PMID: 14663287.

Yong PF, Thaventhiran JE, Grimbacher B. "A rose is a rose is a rose," but CVID is not CVID common variable immune deficiency (CVID), what do we know in 2011? Adv Immunol. 2011;111:47–107. PubMed PMID: 21970952.

License