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ZAP70-Related Combined Immunodeficiency

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Summary

Clinical characteristics

ZAP70-related combined immunodeficiency (*ZAP70*-related CID) is a cell-mediated immunodeficiency caused by abnormal T-cell receptor (TCR) signaling. Affected children usually present in the first year of life with recurrent bacterial, viral, and opportunistic infections, diarrhea, and failure to thrive. Severe lower-respiratory infections and oral candidiasis are common. Affected children usually do not survive past their second year without hematopoietic stem cell transplantation (HSCT).

Diagnosis/testing

The diagnosis of *ZAP70*-related CID is suggested by low to absent $CD8^+$ T cells in an individual with normal CD3+ and CD4+ T-cell counts. Additional supportive laboratory features include absent proliferation of $CD4^+$ T cells in response to mitogens and antigens, and absent ZAP-70 protein expression. The diagnosis is established in a proband by identification of biallelic pathogenic variants in *ZAP70* on molecular genetic testing.

Management

Treatment of manifestations: Supportive care includes immediate intravenous immunoglobulin (IVIG) and antibacterial, antifungal, antiviral, and *Pneumocystis jiroveci* prophylaxis to control and reduce the occurrence of infections.

Prevention of primary manifestations: Allogeneic HSCT to reconstitute the immune system, preferably prior to the onset of infections.

Prevention of secondary complications: Use of irradiated, leukoreduced, cytomegalovirus (CMV)-safe blood products; deferment of immunizations until immune reconstitution; consideration for formula feeds in place of breast feeding until CMV status of mother is known.

Surveillance: Individuals with milder findings or those who have not undergone HSCT need to be monitored for worsening of immune function with periodic assessment of clinical status and functional lymphocyte

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responsiveness. Following a successful HSCT, the following should be routinely monitored: growth, psychomotor development, complete blood counts, liver and renal function, immune status, donor and recipient chimerism, development of post-transplant complications.

Agents/circumstances to avoid: Non-irradiated blood products; live viral, live mycobacterial, and live bacterial vaccinations; contaminated water sources; exposure to fungus-enriched environments (e.g., construction sites, agricultural areas with active soil disruption, mulch, hay).

Evaluation of relatives at risk: Because the outcome of HSCT in children with *ZAP70*-related CID is significantly improved by performing HSCT prior to the onset of severe infections, early testing of at-risk sibs should be considered. In addition, any sibs considered as bone marrow donors must be evaluated for *ZAP70*-related CID prior to donation.

Genetic counseling

ZAP70-related CID is inherited in an autosomal recessive manner. At conception, each sib of an affected individual has a 25% chance of being affected, a 50% chance of being a carrier, and a 25% chance of being unaffected and not a carrier. Carrier testing for at-risk family members and prenatal diagnosis for pregnancies at increased risk are possible if the pathogenic variants in the family are known.

Diagnosis

Suggestive Findings

ZAP70-related combined immunodeficiency (*ZAP70*-related CID) **should be suspected** in individuals who present with the following findings within the first two years of life:

- Recurrent viral, bacterial, and opportunistic infections
- Chronic diarrhea and failure to thrive
- Characteristic results of lymphocyte subset analysis of CD3, CD4, and CD8 T cells, lymphocyte functional testing, and ZAP-70 protein expression (See **Lymphocyte development and numbers**.)

Note: Individuals with non-classic *ZAP70*-related CID may present at an older age with symptoms of autoimmunity, lymphoproliferation, and/or immune dysregulation with or without evidence of immunodeficiency.

Lymphocyte development and numbers. In *ZAP70*-related CID, total lymphocyte counts can range from normal to high.

- Thymic architecture is largely preserved in individuals with *ZAP70*-related CID; however, compared to controls, a smaller medullary zone, decreased numbers of AIRE+ medullary thymic epithelial cells, and decreased numbers of dendritic cell numbers may be seen [Poliani et al 2013].
- T-cell counts:
  - $CD3^+$ cell counts are typically normal.
  - $CD4^+$ cell counts are normal or elevated and may account for 60%-80% of the lymphocytes in individuals with *ZAP70*-related CID. Numbers of CD4+ recent thymic emigrants may be decreased [Hauck et al 2015].
  - $CD8^+$ cells are absent or extremely low, often comprising only 0%-2% of the child's total T-cell count in individuals with *ZAP70*-related CID [Arpaia et al 1994, Noraz et al 2000].
  - Numbers of regulatory T cells may be normal or decreased [Poliani et al 2013, Hauck et al 2015].
- B cell counts and NK cell counts are normal.

Lymphocyte function. T-cell responses to stimuli that act through the T-cell receptor (TCR) are absent or severely diminished:

- Absent or decreased proliferation to CD3 antibody [Roifman et al 2010]
- Absent or decreased proliferation of $CD4^+$ cells in response to mitogens (e.g., PHA, ConA) [Roifman et al 2012]
- Intact proliferative response to mitogenic stimuli that bypass the TCR (e.g., PMA/Ionomycin) [Elder et al 1994, Elder 1997]
- Normal TCR Vβ repertoire in both CD4+ and CD8+ T cells [Roifman et al 2010]
- In CD4 cells: limited differentiation into Th2 cells and resistance to Fas-induced cell death [Roifman et al 2010]
- In regulatory T cells: potentially decreased expression of *CTLA4* and *TGFB* leading to increased risk of autoimmunity [Roifman et al 2010]

ZAP-70 protein expression. Testing of $CD4^+$ T cells reveals absence or near absence of ZAP-70 protein in most affected individuals. Recent reports suggest that the amount of residual ZAP-70 protein expression influences the clinical phenotype [Picard et al 2009, Chan et al 2016, Gavino et al 2017]. Expression of Syk, a related tyrosine kinase important in T-cell signaling, may partially compensate for ZAP-70 signaling in some individuals [Toyabe et al 2001, Hauck et al 2015].

Immunoglobulin concentrations and function

- Immunoglobulin levels vary by individual. Many affected individuals have severe hypogammaglobulinemia, but normal immunoglobulins or elevated IgA, IgM, and/or IgE can also be seen [Turul et al 2009, Cuvelier et al 2016].
- Although functional antibody responses to immunization are present in a few persons [Turul et al 2009, Hauck et al 2015], this finding does not indicate that all specific antigenic responses are intact.

Newborn screening. The utility of TREC screening for individuals with *ZAP70*-related CID continues to be controversial. Although some have shown that TREC levels in individuals with confirmed *ZAP70*-related CID are very low compared to age-matched controls [Roifman et al 2010, Roifman et al 2012, Aluri et al 2017], others have shown that a substantial portion of individuals with *ZAP70*-related CID have TREC levels above the cutoffs used for newborn screening and could be missed [Grazioli et al 2014, Jilkina et al 2014, Hauck et al 2015, Schroeder et al 2016]. Therefore, newborn screening results must be interpreted with caution in individuals with clinical findings consistent with *ZAP70*-related CID or in populations with a high prevalence of *ZAP70*-related CID.

Establishing the Diagnosis

The diagnosis of *ZAP70*-related CID **is established** in a proband by identification of biallelic pathogenic variants in *ZAP70* on molecular genetic testing (see Table 1).

Molecular genetic testing approaches can include **single-gene testing** or use of a **multigene panel**:

- **Single-gene testing.** Sequence analysis of *ZAP70* is performed.

  Note: (1) No deletions or duplications of *ZAP70* have been reported. (2) Targeted analysis for the c.1624-11G>A variant can be performed first in individuals of Mennonite ancestry.

- **A multigene panel** that includes *ZAP70* and other genes of interest (see Differential Diagnosis) may also be considered.

Note: (1) The genes included in the panel and the diagnostic sensitivity of the testing used for each gene varies 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*; thus, clinicians need to determine which multigene panel 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. (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 an introduction to multigene panels click here. More detailed information for clinicians ordering genetic tests can be found here.

Table 1. Molecular Genetic Testing Used in *ZAP70*-Related Combined Immunodeficiency

Gene [1]	Method	Proportion of Probands with Pathogenic Variants [2] Detectable by Method
ZAP70	Sequence analysis [3]	44/44 [4]
	Gene-targeted deletion/duplication analysis [5]	Unknown [6]

1. See Table A. Genes and Databases for chromosome locus and protein.
2. See Molecular Genetics for information on allelic 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. Arpaia et al [1994], Chan et al [1994], Elder et al [1994], Matsuda et al [1999], Meinl et al [2000], Noraz et al [2000], Barata et al [2001], Elder et al [2001], Toyabe et al [2001], Fagioli et al [2003], Picard et al [2009], Turul et al [2009], Santos et al [2010], Newell et al [2011], Hönig et al [2012], Roifman et al [2012], Karaca et al [2013], Kim et al [2013], Grazioli et al [2014], Akar et al [2015], Hauck et al [2015], Cuvelier et al [2016], Esenboga et al [2016], Schroeder et al [2016], Aluri et al [2017], Gavino et al [2017], Shirkani et al [2017]
5. Gene-targeted deletion/duplication analysis detects intragenic deletions or duplications. Methods used may include quantitative PCR, long-range PCR, multiplex ligation-dependent probe amplification (MLPA), and a gene-targeted microarray designed to detect single-exon deletions or duplications.
6. No data on detection rate of gene-targeted deletion/duplication analysis are available.

Clinical Characteristics

Clinical Description

Individuals with *ZAP70*-related CID characteristically present in the first two years of life with recurrent bacterial, viral (including live-virus vaccine strains), and opportunistic infections, diarrhea, and failure to thrive. Severe lower-respiratory infections are seen, most notably *Pneumocystis jiroveci* infections and viral infections. Oral candidiasis is also common [Cuvelier et al 2016, Schroeder et al 2016].

Other presentations have also been reported:

- Reports of milder phenotypes in sibs of children who had died from *ZAP70*-related CID include a child age five months with recurrent lower-respiratory disease but no severe infections [Turul et al 2009] and a child with persistent dermatitis resistant to therapy [Katamura et al 1999].
- A child age nine years with a *ZAP70* hypomorphic intronic pathogenic variant had an attenuated clinical and immunologic phenotype [Picard et al 2009] (see Genotype-Phenotype Correlations).
- A child age 11 months with *ZAP70*-related CID presented with lymphoma [Newell et al 2011].
- BCG-related complications including axillary lymphadenitis or disseminated mycobacterial disease following BCG vaccination may be presenting features [Santos et al 2010, Esenboga et al 2016].

- Two individuals presented with recurrent infections and silent brain infarcts; one also had congenital nephrotic syndrome and autoimmune hemolytic anemia [Akar et al 2015].
- An individual with isolated treatment-refractory immune thrombocytopenia (ITP) has been described [Cuvelier et al 2016].
- Two sibs had refractory autoimmune features including nephrotic syndrome/proteinuria, bullous pemphigoid, and colitis; one also developed autoantibodies to factor VIII caused by a hypomorphic and weakly activating *ZAP70* pathogenic variant [Chan et al 2016].
- An adult with a history of infantile-onset colitis, recurrent respiratory-tract infections, mucocutaneous candidiasis, HSV stomatitis, VZV infection, EBV lymphoproliferative disorder, recurrent CMV viremia, polyomaviremia, and epidermodysplasia verruciformis-like lesions due to HHV-23 was recently reported. A novel pathogenic variant (c.1065C>T) that leads to an altered splice site and low levels of wild-type ZAP-70 protein was identified in this individual [Gavino et al 2017].

The long-term prognosis of untreated *ZAP70*-related CID is death from infection. Affected children have a declining quality of life and usually do not survive past their second year without hematopoietic stem cell transplantation (HSCT).

Genotype-Phenotype Correlations

There is very little genotype-phenotype correlation reported in *ZAP70*-related CID; however, the amount of residual ZAP-70 protein expressed may modulate the clinical phenotype, as suggested by the following:

- A child with a hypomorphic intronic pathogenic variant (c.837+121G>A in intron 7) who had had chronic eczema from age two months and recurrent infections from age two years. The frequency of infections declined at age six following introduction of co-trimoxazole and IVIG prophylaxis. Of note, an older sib with a history of multiple infections had died at age one year [Picard et al 2009].
- Two sibs with refractory autoimmune features including nephrotic syndrome/proteinuria, bullous pemphigoid, and colitis. One sib also developed autoantibodies to factor VIII. These sibs had compound heterozygous *ZAP70* pathogenic variants including a hypomorphic variant (c.574C>T) and a weakly activating variant (c.1079G>C) [Chan et al 2016].

Nomenclature

ZAP70-related combined immunodeficiency may also be referred to as zeta-associated protein 70 deficiency or immunodeficiency 48.

Prevalence

ZAP70-related CID was first described in 1994 in three individuals of Mennonite descent [Arpaia et al 1994]. Since that time, more than 50 affected individuals have been described in the literature [Arpaia et al 1994, Chan et al 1994, Elder et al 1994, Elder et al 1995, Gelfand et al 1995, Katamura et al 1999, Matsuda et al 1999, Meinl et al 2000, Noraz et al 2000, Barata et al 2001, Elder et al 2001, Toyabe et al 2001, Fagioli et al 2003, Picard et al 2009, Turul et al 2009, Santos et al 2010, Newell et al 2011, Hönig et al 2012, Roifman et al 2012, Karaca et al 2013, Kim et al 2013, Grazioli et al 2014, Akar et al 2015, Hauck et al 2015, Cuvelier et al 2016, Esenboga et al 2016, Schroeder et al 2016, Aluri et al 2017, Gavino et al 2017, Shirkani et al 2017].

The prevalence of *ZAP70*-related CID is unknown but much lower than that of all forms of SCID, which is estimated at 1:50,000. Prevalence is higher in the Canadian Mennonite population, where a c.1624-11G>A pathogenic variant resulting in destabilization of the ZAP-70 protein is frequently seen [Arpaia et al 1994, Jilkina et al 2014, Cuvelier et al 2016, Schroeder et al 2016].

Genetically Related (Allelic) Disorders

No phenotypes other than those discussed in this *GeneReview* are known to be associated with pathogenic variants in *ZAP70*.

Differential Diagnosis

Human immunodeficiency virus infection. Infants positive for human immunodeficiency virus (HIV+) may present with recurring infections and failure to thrive similar to CID. Individuals with HIV have $CD4^+$ lymphopenia, in contrast to the $CD8^+$ lymphopenia in individuals with *ZAP70*-related CID. In a neonate, the definitive diagnosis of HIV should be made by detection of cell-associated human immunodeficiency proviral DNA by polymerase chain reaction (PCR) amplification. See Table 2 for additional considerations.

Table 2. Combined Immunodeficiencies in the Differential Diagnosis of *ZAP70*-Related CID

Disorder	Gene Involved	Mode of Inheritance	Lymphocyte Phenotype			
			T	B	NK	Other
ZAP70-related CID	*ZAP70*	AR	+	+	+	$CD4^+/CD8^-$
Familial CD8 deficiency	*CD8A*	AR	+	+	+	$CD4^+/CD8^-$
CD25 deficiency	*IL2RA*	AR	+	+	+	$CD4^-/CD8^+$
MHC II deficiency (BLS)	See **Major histocompatibility complex class II deficiency**.	AR	+	+	+	$CD4^-/CD8^+$

BLS = bare lymphocyte syndrome; MHC II = major histocompatibility complex class II

Familial CD8 deficiency (OMIM 608957) may have a presentation similar to *ZAP70*-related CID; the diagnosis can be confirmed with *CD8A* molecular genetic testing. The two individuals reported with this disease had recurring infections from early childhood and lived past their twenties [de la Calle-Martin et al 2001, Mancebo et al 2008].

CD25 deficiency (OMIM 606367) also presents with recurring infections early in life with low to normal T-cell counts. However, the T cells are $CD4^-/CD8^+$. The diagnosis can be confirmed with molecular genetic testing of *IL2RA* (*CD25*), which encodes the interleukin-2 receptor alpha chain.

Major histocompatibility complex (MHC) class II deficiency (also known as bare lymphocyte syndrome) (OMIM 209920) may have normal or elevated T-cell counts; however, the T cells are $CD4^-/CD8^+$. As in other forms of CID, pathologic findings manifest within the first year of life. Major histocompatibility complex II expression is decreased. Molecular genetic testing may reveal pathogenic variants in *RFX5*, *RFXAP*, *CIITA*, or *RFXANK*, the four genes in which pathogenic variants are known to cause this disorder.

Table 3 differentiates several forms of combined immunodeficiency. Since CID presents as a phenotypically heterogeneous class of diseases, it is useful to recognize forms that present with low to normal T-cell counts. Lymphocyte subset testing and molecular genetic testing can implicate or rule out these other forms of CID.

Table 3. T-Cell-Negative Forms of CID in the Differential Diagnosis of *ZAP70*-Related CID

Disorder	Gene(s) Involved	Mode of Inheritance	Defect	Lymphocyte Phenotype		
				T	B	NK
ZAP70-related CID	*ZAP70*	AR	Decreased protein expression	+	+	+
JAK3-related SCID (OMIM 600802)	*JAK3*	AR		–	+	–
IL7R-related SCID (OMIM 608971)	*IL7R*	AR		–	+	+
CD45 deficiency (OMIM 608971)	*PTPRC*	AR		–	+	–

Table 3. continued from previous page.

Disorder	Gene(s) Involved	Mode of Inheritance	Defect	Lymphocyte Phenotype		
				T	B	NK
ADA deficiency	*ADA*	AR	Decreased protein production	–	–	–
RAG1/2 deficiency (OMIIM 601457)	*RAG1*, *RAG2*	AR		–	–	+
SCID Athabascan (OMIM 602450)	*DCLRE1C*	AR		–	–	+
X-linked SCID	*IL2RG*	XL	Dysfunctional receptor	–	+	–

Omenn syndrome (OMIM 603554). Some individuals with *ZAP70*-related CID can present with Omenn syndrome-like features including rash, lymphadenopathy, hepatosplenomegaly, and eosinophilia.

Management

Evaluations Following Initial Diagnosis

The care of individuals diagnosed with *ZAP70*-related CID is best managed with a multidisciplinary team of providers including hematology/oncology/bone marrow transplantation, immunology, genetics, and infectious disease specialists. To establish the extent of disease and needs in an individual diagnosed with *ZAP70*-related combined immunodeficiency (CID), the following evaluations are recommended:

- Assessment of growth
- Evaluation for common and opportunistic viral, bacterial, and fungal disease-causing agents
- Complete metabolic panel (liver and renal function), complete blood count (CBC) with differential and platelet count, lymphocyte subsets and mitogen proliferation, and quantitative immunoglobulins
- Consultation with a clinical geneticist and/or genetic counselor
- Consultation with a clinical immunologist
- Consultation for hematopoietic stem cell transplantation

Treatment of Manifestations

Treatment relies on prompt reconstitution of the individual's immune system (see Prevention of Primary Manifestations).

Supportive treatment includes IVIG and antibacterial, antifungal, antiviral, and *Pneumocystis jiroveci* prophylaxis to control and reduce the occurrence of infections.

Prevention of Primary Manifestations

The only curative therapy for *ZAP70*-related CID is allogeneic hematopoietic stem cell transplantation (HSCT). Extrapolated data show that the outcome of HSCT in children with SCID is significantly improved by performing HSCT prior to the onset of infections [Pai et al 2014]. Children with *ZAP70*-related CID have been successfully transplanted using a variety of donors including haploidentical donors and unrelated umbilical cord blood [Noraz et al 2000, Elder et al 2001, Hönig et al 2012, Cuvelier et al 2016].

- Outcomes are the best with HLA-matched, related donors.
- If an HLA-matched, related donor is not available, alternatives include:
  - Matched unrelated donor;
  - Umbilical cord blood donor;
  - Haploidentical parental bone marrow or mobilized peripheral blood stem cells that have been T-cell depleted.

- In contrast to individuals with SCID, individuals with *ZAP70*-related CID are typically treated with a chemotherapeutic conditioning regimen prior to HSCT, although some individuals have received unconditioned transplants with variable success, suggesting that conditioning may not be essential in some circumstances [Hönig et al 2012, Kim et al 2013, Cuvelier et al 2016].
- The largest series of eight individuals with *ZAP70*-related CID who received HSCT using a variety of stem cell sources showed the following:
  - All individuals were alive at a median of 13.5 years of follow up.
  - Two-thirds of the individuals who did not receive conditioning failed to have myeloid engraftment but have maintained stable mixed chimerism. In addition, three individuals who received stem cells from a matched sib did not receive conditioning prior to transplant and achieved engraftment.
  - 75% of individuals developed acute graft-versus-host disease (GVHD) and 50% developed chronic GVHD.
  - Seven of eight individuals achieved freedom from IVIG and show evidence of class switching with resolution of dysregulated immunoglobulin production and six of the eight show evidence of antibody production to both protein and polysaccharide vaccines.
  - Two individuals receiving myeloablative conditioning have developed premature ovarian failure.
- Cellular reconstitution following HSCT takes up to one year, while restoration of humoral immunity can take significantly longer, and may not occur in some individuals.
- Complications from HSCT include graft-versus-host disease, failure to reconstitute the humoral immune compartment, graft failure over time, and post-transplant lymphoproliferative disease [Skoda-Smith et al 2001, Dvorak & Cowan 2008, Pai et al 2014].
- Affected individuals with poor humoral reconstitution are maintained on long-term immunoglobulin replacement.

Individuals who do not undergo HSCT require close monitoring for worsening of immune function manifested by increased susceptibility to severe or opportunistic infections (see also Surveillance). If clinical status worsens, rapid transition to HSCT should be considered.

Prevention of Secondary Complications

The following are appropriate:

- Use of irradiated, leukoreduced, cytomegalovirus (CMV)-safe blood products
- Delay of immunizations until immune reconstitution
- Consideration for formula feeds in place of breast feeding until CMV status of mother is known. Caution should be taken to assess the quality of the water source for the infant formula.

Surveillance

Following a successful HSCT, the following should be routinely monitored:

- Growth
- Psychomotor development
- Complete blood counts
- Liver and renal function
- Immune status
- Donor and recipient chimerism
- Development of post-transplant complications, particularly chronic graft-versus-host disease, decreased bone density, pulmonary and cardiac function, and gonadal function

Individuals with milder findings or those who have not undergone HSCT also need to be monitored for worsening of immune function with periodic assessment of clinical status and functional lymphocyte responsiveness.

Agents/Circumstances to Avoid

Individuals with *ZAP70*-related CID should avoid the following:

- Non-irradiated blood products
- Live virus vaccinations
- *Mycobacterium bovis* (BCG) vaccine against tuberculosis, *Salmonella typhi* (Ty21a) vaccine against typhoid fever, and *Vibrio cholerae* (CVD 103-HgR) vaccine against cholera, which may be part of the routine vaccination schedule in countries where these diseases are endemic
- Contaminated water sources
- Exposure to fungus-enriched environments (e.g., construction sites, agricultural areas with active soil disruption, mulch, hay)

Evaluation of Relatives at Risk

Because the outcome of HSCT in children with *ZAP70*-related CID is significantly improved by performing HSCT prior to the onset of severe infections, early testing of at-risk sibs should be considered. In addition, any sibs considered as bone marrow donors must be evaluated for *ZAP70*-related CID prior to donation.

- If the *ZAP70* pathogenic variants in the family are known, molecular genetic testing can be used to clarify the genetic status of at-risk sibs.
- If the pathogenic variants in the family are not known, CBC, quantitative immunoglobulins, and lymphocyte subsets and proliferation can be used to clarify the genetic status (immunologic status) of at-risk sibs.

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

Pregnancy Management

Appropriately screened blood products should be available, if needed, during the course of the pregnancy and delivery.

Therapies Under Investigation

Gene therapy. Gene therapy has not been performed in *ZAP70*-related CID. Experimental studies utilizing gene therapy have been conducted on murine models [Adjali et al 2005, Irla et al 2008] as well as human cells in vitro [Steinberg et al 2000, Kofler et al 2004, Gavino et al 2017]. Nonviral transfer methods (e.g., electro-gene transfer) have also been used to correct ZAP-70 deficiency in a murine model [Irla et al 2008].

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

ZAP70-related combined immunodeficiency (CID) is inherited in an autosomal recessive manner.

Risk to Family Members

Parents of a proband

- The parents of an affected child are obligate heterozygotes (i.e., carriers of one *ZAP70* pathogenic variant).
- Heterozygotes usually do not have CID-like symptoms. Parents of probands who did not appear to have clinical symptoms had intermediate expression levels compared to healthy controls [Turul et al 2009]. Further studies suggested a ZAP-70 protein level threshold effect, which may explain why parents with decreased *ZAP70* expression may have no clinical features [Cauwe et al 2014].

Sibs of a proband

- At conception, each sib of an affected individual has a 25% chance of being affected, a 50% chance of being a carrier, and a 25% chance of being unaffected and not a carrier.
- Even if the sibs of a proband are asymptomatic, molecular genetic testing to determine their genetic status should be considered for the purpose of early diagnosis and treatment of those who have inherited both pathogenic variants (see Evaluation of Relatives at Risk).

Offspring of a proband

- The offspring of an individual with *ZAP70*-related CID will inherit one pathogenic variant from the proband.
- The genetic status of the offspring will depend on the genetic status of the reproductive partner of the proband.
  - If the reproductive partner is not affected and not a carrier, all offspring will be carriers.
  - If the reproductive partner is a carrier of a *ZAP70* pathogenic variant, each child will have a 50% chance of being affected and a 50% chance of being a carrier.
  - If the reproductive partner is also affected, all offspring will be affected.

Other family members. A detailed family history that includes the ancestry and culture of the proband's family may reveal consanguinity and geographic and genetic isolation – risk factors that increase the likelihood of autosomal recessive diseases in a family. Some of the grandparents of the proband are carriers of a *ZAP70* pathogenic variant; therefore, sibs of the proband's parents and their offspring are at risk of being carriers.

Carrier (Heterozygote) Detection

Carrier testing for at-risk relatives requires prior identification of the *ZAP70* pathogenic variants in the family.

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 carrier 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 carriers, or are at risk of being carriers.

Prenatal Testing and Preimplantation Genetic Testing

Once the *ZAP70* pathogenic variants have been identified in an affected family member, prenatal testing for a pregnancy at increased risk and preimplantation genetic testing for *ZAP70*-related CID are possible.

An affected fetus does not require any specific management prior to delivery. Following delivery, early evaluation for potential HSCT should be performed because of the known benefit of early HSCT (see Evaluation of Relatives at Risk).

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.

- **International Patient Organization for Primary Immunodeficiencies (IPOPI)**
  United Kingdom
  Phone: +44 01503 250 668
  Fax: +44 01503 250 668
  Email: info@ipopi.org
  ipopi.org
- **Jeffrey Modell Foundation/National Primary Immunodeficiency Resource Center**
  Email: info@jmfworld.org
  info4pi.org
- **ImmUnity Canada**
  Canada
  Phone: 250-381-7134; 877 -607-2476
  Email: info@immunitycanada.org
  immunitycanada.org
- **National Human Genome Research Institute (NHGRI)**
  Learning About Severe Combined Immunodeficiency (SCID)
- **NCBI Genes and Disease**
  Severe combined immunodeficiency
- **European Society for Immunodeficiencies (ESID) Registry**
  Email: esid-registry@uniklinik-freiburg.de
  ESID Registry
- **RDCRN Patient Contact Registry: Primary Immune Deficiency Treatment Consortium**
  Patient Contact 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. ZAP70-Related Combined Immunodeficiency: Genes and Databases

Gene	Chromosome Locus	Protein	Locus-Specific Databases	HGMD	ClinVar
ZAP70	2q11.2	Tyrosine-protein kinase ZAP-70	ZAP70 database ZAP70base: Mutation registry for autosomal recessive ZAP70 immunodeficiency	ZAP70	ZAP70

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 ZAP70-Related Combined Immunodeficiency (View All in OMIM)

176947	ZETA-CHAIN-ASSOCIATED PROTEIN KINASE; ZAP70
269840	IMMUNODEFICIENCY 48; IMD48

Gene structure. *ZAP70* spans 26.3 kb of genomic DNA. The gene consists of 14 exons comprising 2450 bp. For a detailed summary of gene and protein information, see Table A.

Pathogenic variants. *ZAP70* pathogenic variants reside mostly in the kinase domain, although pathogenic variants that result in loss of transcription or are located in the N-terminal SH2 domain and result in rapid degradation of ZAP-70 protein have been reported [Matsuda et al 1999, Au-Yeung et al 2009]. More than 20 pathogenic variants including single-nucleotide variants, splice defects, and intragenic deletions have been reported. A pathogenic variant in the arginine residue (p.Arg465Cys) of the DLAARN motif of the kinase domain has been described (see **Abnormal gene product**).

Table 4. *ZAP70* Pathogenic Variants Discussed in This *GeneReview*

DNA Nucleotide Change (Alias [1])	Predicted Protein Change	Reference Sequences
c.239C>A (448C>A)	p.Pro80Gln	NM_001079.3 NP_001070.2
c.574C>T	p.Arg192Trp	
c.837+121G>A (836+121G>A)		
c.1079G>C	p.Arg360Pro	
c.1393C>T	p.Arg465Cys	
c.1624-11G>A		
c.1714A>T (1923A>T)	p.Met572Leu	
c.1065C>T (c.1272C>T)	See footnote 2.	NM_001079.4 NP_001070.2

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.
1. Variant designation that does not conform to current naming conventions
2. The variant is predicted to be silent (p.Gly355=) but has been demonstrated to result in a splicing defect [Gavino et al 2017].

Normal gene product. *ZAP70* codes for a 619-amino acid enzyme, ZAP-70, that contains two SH2 domains and one kinase domain. This Syk-protein tyrosine kinase family member plays a role in T cell development and activation. ZAP-70 directly interacts with the T-cell receptor (TCR) complex and is phosphorylated at tyrosine

residues upon TCR stimulation, functioning in the initial step of TCR-mediated signal transduction with Src family kinases.

Abnormal gene product. Most pathogenic variants affect the kinase domain of *ZAP70* and cause a lack of or severely decreased protein expression. Loss of ZAP-70 activity leads to lack of signaling through the T-cell receptor and subsequent defects in CD8+ cell development and in global T-cell function [Fischer et al 2010].

The residual function seen in CD4 and CD8 cells in individuals lacking ZAP-70 may be related to increased expression of Syk in affected cells [Hauck et al 2015]. In ZAP-70-deficient CD4+ cells, TCR stimulation was able to induce antigen-specific IgE responses in B cells in part via increased expression of Syk [Toyabe et al 2001].

Chapter Notes

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Revision History

- 23 September 2021 (sw) Revision: nucleotide variant correction: c.1065C>T
- 8 June 2017 (sw) Comprehensive update posted live
- 25 September 2014 (me) Comprehensive update posted live
- 6 September 2012 (cd) Revision: prenatal diagnosis available clinically
- 1 March 2012 (me) Comprehensive update posted live
- 20 October 2009 (me) Review posted live
- 1 June 2009 (tc) Original submission

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