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Common Variable Immune Deficiency Overview

[*CVID, Combined Variable Immune Deficiency*]

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Summary

Disease characteristics. Common variable immune deficiency (CVID) is characterized by humoral immune deficiency with onset after 24 months of age and usually in young adulthood, resulting in increased susceptibility to infections and diminished responses to protein and polysaccharide vaccines. The most common infections are sinopulmonary and include *Streptococcus* pneumonia, *Hemophilis* influenza, *Klebsiella* pneumonia, and sometimes mycoplasma infections. Individuals may experience meningitis or other systemic bacterial infections, recurrent eye or skin infections, or gastrointestinal symptoms related to compromised immune/gut homeostasis, including chronic diarrhea, malabsorption, or bloating. They may also have abnormal T-cell function and immune dysregulation, including lymphoid hyperplasia, gastrointestinal inflammation, autoimmune phenomena, and susceptibility to malignancy, especially lymphomas.

Diagnosis/testing. The diagnosis of CVID is primarily established by testing for low serum IgG concentration ranging from profoundly reduced (<100 mg/dL) to just below adult normal range (500-1200 mg/dL). Individuals often manifest a functional defect in IgG responses to immunization by Pneumovax and Bacteriophage ΦX174. Other abnormal laboratory studies include reduced serum concentrations of other immunoglobulins, especially IgA or IgM, and reduced numbers of switched memory B-cells as assessed by peripheral B-cell immunophenotyping. Abnormal laboratory or imaging studies include abnormalities in T-cell

memory subsets on T-cell immunophenotyping; in vitro proliferative responses of peripheral blood lymphocytes to a general mitogen, crosslinking of CD3, or activation with specific antigens; deficient cytokine production by peripheral blood lymphocytes; nodular lymphoid hyperplasia on x-ray, enteroscopy, or intestingal biopsies; and evidence of non-caseating granulomas on imaging or biopsy. Testing for loss of protein expression is clinically available for *TACI*-, *CD19*- and *BAFFR*-associated CVID. Molecular genetic testing for the *TNFRSF13B (TACI*) gene (found in 10-15% of individuals with CVID) and the *ICOS* gene (found in 1% or fewer of individuals with CVID) is clinically available.

Management. Treatment for CVID includes starting immune globulin replacement therapy to provide protective antibodies as soon as possible, appropriate treatment with antibiotics, and treatment as appropriate for autoimmune phenomena. To prevent recurrent sinopulmonary infections and prevent chronic lung disease, purified immune globulin is administered intravenously and subcutaneously and prophylactic antibiotics are given. Antibiotics may help control small bowel bacterial overgrowth. Surveillance includes periodic CBC and differential WBC counts to detect lymphoma, annual thyroid examination and thyroid function testing, annual pulmonary function testing beginning about age eight to ten years, high-resolution CT scan every two to three years to follow progression of lung disease, biopsy of enlarged lymphoid tissue, and other imaging techniques for assessment of granulomatous disease and GI complications. Clinical surveillance of asymptomatic at-risk individuals may allow timely intervention and improve outcome. Use of molecular genetic testing for early identification of at-risk family members may improve diagnostic certainty; however, as genetic causes of CVID are rare and undergoing investigation, careful consideration of genetic testing is warranted on a case-by-case basis for each family. It is prudent for individuals with bronchiectasis to avoid contact with peat or other sources of aspergillus.

Genetic counseling. CVID can be inherited in an autosomal dominant or autosomal recessive manner. In families in which CVID is inherited in an autosomal dominant manner, the sibs of an affected individual have a 50% chance of inheriting the mutation assuming that one parent has a disease-causing mutation. In families in which CVID is inherited in an autosomal recessive manner, the parents of an affected individual are most like heterozygotes (usually asymptomatic) and each carries one mutant allele. At conception, each sib of an affected individual has a 25% chance of being affected, a 50% chance of being an asymptomatic carrier, and a 25% chance of being unaffected and not a carrier. Carrier testing and prenatal diagnosis for pregnancies at increased risk for *TACI*-associated CVID and *ICOS*-associated CVID are available on a clinical basis once the mutations have been identified in the proband.

Definition

Clinical Manifestations

The term "**c**ommon **v**ariable **i**mmune **d**eficiency" (CVID) is an umbrella diagnosis used for the clinical presentation of "late onset" humoral immune deficiency. "Late onset" is loosely defined as after 24 months of age; although the most common presentation is in young adults, onset after age 24 months is a criterion for making a formal diagnosis of CVID as defined by the European Society for Immunodeficiency (ESID) and the Pan American Group for Immunodeficiency (PAGID) [Conley et al 1999]. The "CVID" phenotype is thought to result primarily from heterogeneous single or multiple gene defects that detrimentally affect humoral immune function.

Immune deficiency. CVID by definition involves a clinically significant deficit in humoral immune function, which directly leads to increased susceptibility to infections and diminished responses to protein and polysaccharide vaccines. The most commonly reported infections are sinopulmonary, and the bacteria most often associated with recurrent sinopulmonary infections

in CVID are *Streptococcus* pneumonia, *Hemophilus* influenza, and *Klebsiella* pneumonia. Recurrent sinopulmonary infections may begin anytime after age two years, but more commonly are preceded by a long time period (e.g., decades) in which infection frequency and severity are normal or near normal. Some individuals with CVID may also have difficulty in protecting themselves from mycoplasma infections [Foy et al 1973, Gelfand 1993]. Variably, individuals with CVID may also have experienced meningitis or other systemic bacterial infections, recurrent eye or skin infections, or gastrointestinal (GI) symptoms related to compromised immune/gut homeostasis, including chronic diarrhea, malabsorption, or bloating.

While most clinical manifestations of CVID are related to humoral immune dysfunction, individuals with CVID may also exhibit symptoms of abnormal T-cell function and immune dysregulation, including lymphoid hyperplasia, gastrointestinal inflammation, a variety of autoimmune phenomena, and a susceptibility to malignancy, especially lymphomas [Cunningham-Rundles & Bodian 1999; Cunningham-Rundles 2001; Piqueras et al 2003; Di Renzo et al 2004; Kokron et al 2004; Aghamohammadi et al 2005; Santaella, Cox et al 2005].

Gastrointestinal (GI) pathology. Infections and inflammation with associated malabsorptive symptoms have been reported in about 20% of individuals with CVID [Cunningham-Rundles & Bodian 1999]. GI infections with *Salmonella*, *Campylobacter*, or *Giardia* occur in about 10% of individuals [Cunningham-Rundles & Bodian 1999, Piqueras et al 2003, Wang et al 2004, Aghamohammadi et al 2005]. The lifetime risk for any individual may be 25% or higher [HD Ochs, unpublished observations], and is probably directly related to the nature and severity of the humoral immune defect.

H. pylori infection has been reported in over 40% of dyspeptic individuals with CVID. Enhanced susceptibility to *H. Pylori* may result from both lack of humoral immunity and absence of B-cells and IgA plasma cells in the gastric mucosa of individuals with CVID who have gastritis [Zullo et al 1999].

Disturbances in gut immune/bacterial symbiosis and homeostasis are thought to contribute to chronic gut inflammation and associated malabsorption (sprue-like disease not responsive to gluten withdrawal) present in about 2-3% of individuals with CVID. These symptoms are in many cases responsive to antibiotic treatment and so are thought to be in part a result of chronic small intestinal bacterial overgrowth.

GI inflammation in individuals with CVID may also resemble Crohn's disease (about five percent of individuals) or ulcerative colitis (about two percent) [Cunningham-Rundles & Bodian 1999]. A subset of individuals with CVID exhibit nodular lymphoid hyperplasia on GI imaging studies, although this is not generally thought to be a significant cause of GI-related symptoms unless it is associated with *Giardia* infection.

Autoimmune phenomena. Twenty to twenty-five percent of individuals exhibit one or more diverse forms of autoimmune-related phenomena, ranging from disorders resembling rheumatoid arthritis and systemic lupus erythematosus to various blood cytopenias, hepatitis, and alopecia areata [Cunningham-Rundles & Bodian 1999; Piqueras et al 2003; Wang et al 2004; Aghamohammadi et al 2005; Castigli et al 2005; Salzer et al 2005; Santaella, Cox et al 2005]. Autoimmune thrombocytopenia and anemia are most commonly reported (about 4-5% and 2-4%, respectively) [Cunningham-Rundles & Bodian 1999].

While individuals with CVID may possess autoantibodies and symptoms typically associated with specific autoimmune pathologies (e.g., rheumatoid factor with arthritis, anti-nuclear antibodies with lupus-like symptoms), the diagnostic and prognostic significance of the

presence or absence of autoantibodies is less clear in the context of CVID than in individuals without immune defects [Swaak & van den Brink 1996; Uluhan et al 1998; Lin et al 2005; Santaella, Cox et al 2005; Sordet et al 2005; Swierkot et al 2006].

Non-caseating granulomas have been reported in 8-20% of individuals with CVID [Cunningham-Rundles & Bodian 1999, Goldacker & Warnatz 2005, Morimoto & Routes 2005, Knight & Cunningham-Rundles 2006]. Evidence of active human herpes virus 8 (HHV8) infection can be found in the peripheral blood monocytes of a high proportion of individuals with CVID with granulomatous and interstitial lung disease [Wheat et al 2005], consistent with the association of HHV8 with lymphoproliferative phenomena in persons with secondary immunodeficiencies and hematological malignancies [Aoki & Tosato 2003, Viejo-Borbolla & Schulz 2003, Viejo-Borbolla et al 2004, Collins et al 2006].

The autoimmune phenomena experienced by individuals with CVID are presently viewed as caused by immune dysregulation occurring secondary to the molecular defect underlying their humoral immune deficiency. The onset and severity of autoimmune phenomena in any individual with CVID are therefore likely to be heavily influenced by other genetic immune modifiers such as their **m**ajor **h**istocompatibility **c**omplex (MHC) haplotype as well as environmental influences including virus and GI pathogen exposure and the presence or absence of chronic inflammation.

Malignancy. Individuals with CVID are susceptible to malignancy, particularly lymphoma. In their series of 248 individuals, Cunningham-Rundles & Bodian (1999) found that nearly eight percent developed non-Hodgkins lymphoma (NHL); another one to two percent had Hodgkins lymphoma; and other individuals had 24 different cancers, including breast cancer, prostate cancer, squamous cell carcinoma, melanoma, and basal cell carcinoma.

Implications for prognosis. In the past, the primary determinant of the long-term prognosis for individuals with CVID was the number and severity of bacterial sinopulmonary infections, contributing to an overall mortality rate of 23-30% over approximately ten year follow-up periods [Cunningham-Rundles & Bodian 1999; Thickett et al 2002; Stiehm et al 2004; Wang et al 2004, Aghamohammadi et al 2005; Santaella, Font et al 2005].

Because of the prominent role that infections have played in the morbidity experienced by individuals with CVID, the long term outcome of individuals with CVID is expected to improve in the future with the increasingly aggressive use of intravenous or subcutaneous immune globulin therapy and antibiotics for infection treatment and prophylaxis. Consequently, it is likely that published data on the long-term morbidity and mortality of CVID underestimate how well newly-diagnosed individuals with CVID may be expected to do with current therapies and close follow-up with an experienced immunologist.

One implication of a decrease in infection-associated morbidity and mortality for individuals with CVID will be a likely increase in morbidity and mortality secondary to autoimmune diseases and malignancy, as increased life span provides additional time and opportunities for immune dysregulation and chronic low-level inflammation to cause cumulative damage, or to allow the outgrowth of autoreactive lymphocytes or malignant lmphoid or gastrointestinal cells.

Establishing the Diagnosis of CVID

Low serum IgG concentration. The most important laboratory criterion for establishing the diagnosis of CVID is a low serum IgG concentration, ranging from profoundly reduced (<100 mg/dL) to just below the adult normal range of 500-1200 mg/dL.

Note: Total serum concentration of IgG may trend downward over time, such that a single normal serum IgG concentration does not exclude a diagnosis of CVID in an individual experiencing frequent infections.

Functional defect in IgG responses to immunization. Individuals with CVID often manifest a functional defect in IgG responses to immunization.

While responses to protein antigens such as the diphtheria or tetanus components of the DT vaccine may be reduced, they are often preserved as a result of the high immunogenicity of these vaccines, particularly in individuals diagnosed relatively soon after the onset of frequent infections [Al-Herz & McGeady 2003]. Responses to Pneumovax, the 23-valent pneumococcal polysaccharide vaccine, and Bacteriophage ΦX174 are more frequently abnormal because of the lower immunogenicity of these vaccines.

Other abnormal laboratory studies often found in CVID:

- **Reduced serum concentrations of other immunoglobulins, especially IgA or IgM**
- **Reduced numbers of switched memory B-cells as assessed by peripheral B-cell immunophenotyping.** The switched memory B-cell subset $CD27^{hi}/IgM^{lo}/IgD^{lo}$ [Tangye et al 1998] are B-cells that have been activated and gone through a germinal center reaction to become isotype switched. From 50-75% of individuals with CVID have reduced numbers of switched memory B-cells [Agematsu et al 2002, Warnatz et al 2002, Piqueras et al 2003, Ko et al 2005]

Abnormal laboratory or imaging studies which may occur in CVID:

- **Abnormalities in T-cell memory subsets** on T-cell immunophenotyping. The most typical pattern is a low CD4 count associated with a normal to increased CD8 count [Baumert et al 1992, Holm et al 2004].
- **In-vitro proliferative responses of peripheral blood lymphocytes** to a general mitogen such as phytohemagglutinin, crosslinking of CD3, or activation with specific antigens such as tetanus or candida. About 20% of individuals with CVID have reduced responses, often in association with reduced CD4 T-cell counts [Eisenstein et al 1993; Jaffe, Eisenstein et al 1993; Jaffe, Strober et al 1993].
- **Deficient cytokine production by peripheral blood lymphocytes** (various cytokines in diverse assays, reviewed in Cunningham-Rundles (2002) and Salzer & Grimbacher (2005)
- **Nodular lymphoid hyperplasia** on x-ray, enteroscopy, or intestinal biopsies
- **Evidence of non-caseating granulomas** on imaging studies or biopsy, most commonly observed in the lung, spleen, liver, and skin, but which may occur in any tissue

Normal results are typically obtained on the following immunologic tests:

- Neutrophil function, such as oxidative burst testing
- Serum complement concentration

Differential Diagnosis of CVID

Disorders with hypo- or agammaglobulinemia or functional antibody deficiency as a primary component:

- **X-linked agammaglobulinemia (XLA).** XLA is caused by inactivating mutations in the gene, *BTK*, which encodes Bruton's tyrosine kinase (BTK). XLA is

characterized by a marked reduction in all classes of serum immunoglobulins and absent B cells (CD19+ cells). The decrease in the number of B cells is the most consistent and distinctive feature of XLA, and typically B-cell numbers are reduced to a greater extent in individuals with XLA than in those with CVID. XLA usually presents with recurrent bacterial infections in affected males in the first two years of life; less commonly, XLA may present later in life with a presentation identical to classic CVID. Specific *BTK* mutations have not been consistently found to be associated with an atypical presentation or milder clinical course [Holinski-Feder et al 1998], although recent data suggest that mutations that allow some protein expression are associated with higher B-cell numbers, high IgM levels, and an older age of diagnosis [Broides et al 2006]. Therefore, unknown modifying factors may be important determinants of the clinical manifestations associated with particular *BTK* mutations.

- **X-linked lymphoproliferative disease (XLP).** XLP is caused by mutations in the gene, *SH2D1A*, which encodes the protein SH2D1A. XLP most commonly presents with lymphoproliferative manifestations, and less commonly, with a CVID-like picture following an acute EBV infection [Morra et al 2001]. The three main manifestations of classic XLP are (1) an inappropriate immune response to Epstein-Barr virus (EBV) infection, resulting in unusually severe and often fatal infectious mononucleosis associated with widespread proliferation of cytotoxic T cells, EBV-infected B cells, and macrophages; (2) dysgammaglobulinemia (i.e., hypogammaglobulinemia of one or more immunoglobulin subclasses); and/or (3) lymphoproliferative disorders, typically of B-cell origin, such as high grade B-cell lymphomas, non-Hodgkin type, often extra-nodal, and particularly involving the intestine. Specific *SH2D1A* mutations have not been found to be associated with an atypical presentation or milder clinical course [Nistala et al 2001, Parolini et al 2002, Soresina et al 2002, Aghamohammadi et al 2003]. Rather, it appears that unknown modifying factors determine how a particular *SH2D1A* mutation behaves in a given individual.

- **Autosomal recessive agammaglobulinemias.** These disorders include mutations in the μ immunoglobulin heavy chain gene *(IGHM)*, the λ5 light chain gene *(IGLL1)*, the B-cell linker protein gene *BLNK*, and Igα *(CD79A)*. All individuals reported have presented with severe agammaglobulinemia in association with very low or absent B-cell numbers [Conley 2002]. As for XLA, B-cell numbers in individuals with these disorders are reduced to a greater extent than is typically observed in individuals with CVID.

- **Combined immune deficiencies.** These include, e.g., ataxia-telangiectasia*(ATM)*, polynucleotide phosphorylase *(NP* gene) or adenosine deaminase *(ADA)* deficiency.

- **Wiskott-Aldrich syndrome (WAS).** WAS is caused by inactivating mutations in the gene, *WAS*, which encodes the Wiskott-Aldrich syndrome protein (WASP). However, the characteristic symptoms of eczema, thrombocytopenia, and bloody diarrhea should help to distinguish WAS from CVID.

- **Warts/hypogammaglobulinemia/infection/myelokathexis (WHIM) syndrome.** This syndrome is caused by carboxy-termini truncating mutations in the gene *CXCR4* that encodes a chemokine receptor. It should be suspected in individuals being evaluated for CVID who have a history of marked susceptibility to cutaneous papilloma virus infections.

Complement deficiencies. Various deficiencies in components of the alternative or classic pathways may present with recurrent encapsulated bacterial infections in a picture resembling CVID. Such individuals are usually readily distinguishable from those with CVID by their

normal T-cell and B-cell numbers and by their deficiency in general and specific measures of complement function.

Hyper IgM syndromes may have a similar clinical presentation to CVID. A low IgM level (<20 mg/dL) may help differentiate CVID from the hyper IgM syndromes, in which serum concentration of IgM is typically normal to elevated. At least five genetically distinct forms are recognized; all have a defect in the molecular mechanisms involved in class switch recombination and somatic hypermutation:

- **X-linked HIGM,** caused by inactivating mutations in:
  - The gene encoding the CD40 ligand *(CD40LG*)
  - The gene *IKBKG (NEMO*) encoding **N**F-kappa-B **e**ssential **mo**dulator. Affected males have hypomorphic mutations resulting in impaired, but not absent, NF-kappa-B signaling. They can be distinguished from classic CVID by the dermatologic signs of hypohydrotic ectodermal dysplasia. Mutations in *IKBKG* leading to loss of function cause incontinentia pigmenti in heterozygous females (and are lethal in males).
- **Autosomal recessive HIGM,** caused by inactivating mutations in:
  - The gene encoding CD40 *(CD40*)
  - The gene encoding activation-induced cytidine deaminase *(AID*)
  - The gene encoding uracil DNA N-glycosylase *(UNG*)

Recognizable syndromes or disorders that may include hypogammaglobulinemia or functional humoral immune deficiency in association with abnormalities in other organ systems:

- Netherton syndrome, caused by inactivating mutations in the gene SPINK5, encoding serine protease. Netherton syndrome is easily distinguished from classic CVID by the prominent dermatologic symptoms.
- Down syndrome
- 22q11.2 deletion syndrome
- Kabuki syndrome
- CHARGE syndrome *(CHD7* gene)
- Intestinal lymphangiectasia and lymphatic malformations

Other common syndromes associated with chronic or recurrent bacterial pneumonia or bronchiectasis:

- Cystic fibrosis
- Immotile cilia syndrome
- Leukocyte adhesion deficiencies (LAD): LAD I caused by mutations in the gene encoding the CD18 protein *(ITGB2*); LAD II or congenital disorder of glycosylation, CDG IIc, caused by mutations in the *SLC35C1* gene; and LAD III (gene unidentified) (see Congenital Disorders of Glycosylation Overview)
- Congenital neutropenias including *ELA2*-related neutropenia and that seen in *WAS*-related disorders (X-linked severe congential neutropenia)
- Chronic granulomatous disease (CGD)

- Autoimmune lymphoproliferative syndrome (ALPS) (defects in caspase 8, *CASP8*)

Other syndromes associated with chronic or protracted diarrhea in childhood or early adulthood:

- Microvillus inclusion disease
- Tufting enteropathy
- Autoimmune enteropathies including immune dysregulation, polyendocrinopathy, enteropathy, X-linked (IPEX)

Drug induced. Hypogammaglobulinemia may rarely occur in association with treatment with anti-malarial agents, captopril, carbamazepine, glucocorticoids, fenclofenac, gold salts, penicillamine, phenytoin, and sulfasalazine.

"Secondary hypogammaglobulinemia." An important diagnostic consideration in adults who present with a CVID picture is lymphoid neoplasias, such as chronic lymphocytic leukemia or multiple myeloma.

Prevalence

Overall prevalence is approximately one in 30,000 live births [Stiehm et al 2004].

Causes

Heritable Causes

A significant fraction of CVID is now thought to result from heterogeneous single or multiple gene defects that detrimentally affect humoral immune function. Approximately 10-20% of individuals have an identified heritable cause of CVID (Table 1A and Table 1B).

Note: As individuals with a clinical presentation of CVID may have mutations in molecularly defined immunodeficiencies such as XLA or XLP, excluding these diagnoses by DNA testing is an important component of the CVID diagnostic workup.

Molecular Genetics

Table 1A. Molecular Genetics of Heritable Causes of CVID: Established

% of Individuals with CVID	Mode of Inheritance	Disease Name	Gene Symbol	Chromosomal Locus	Protein Name
Up to 10-15%	AD	*TACI*-associated CVID	*TNFRSF13B (TACI)*	17p11.2	Tumor necrosis factor receptor superfamily member 13B
1% or less	AR	*ICOS* deficiency	*ICOS*	2q33	Inducible T-cell co-stimulator
<1%	AR	*CD19* deficiency	*CD19*	16p11.2	B-lymphocyte antigen CD19

Table 1B. Molecular Genetics of Heritable Causes of CVID: Pending

% of Individuals with CVID	Mode of Inheritance	Disease Name	Gene Symbol	Chromosomal Locus	Protein Name
<1%	AR	*BAFFR* deficiency	*TNFRSF13C (BAFFR)*	22q13.1-q13.3	Tumor necrosis factor receptor superfamily member 13C
75-80%		Currently unknown			

Note:*GeneReviews* uses the following standard sources: Gene symbol, HUGO; chromosomal locus, OMIM; protein name, Swiss Prot.

Kanegane et al 2000, Nistala et al 2001, Weston et al 2001, Soresina et al 2002, Aghamohammadi et al 2003, Eastwood et al 2004, Salzer et al 2004, Stiehm et al 2004, Castigli et al 2005, Salzer et al 2005

TACI encodes a B-cell immunoregulatory cell surface molecule of the TNF receptor superfamily, transmembrane activator, and CAML interactor.

To date, six different *TACI* mutations (Q68X, C104R, S144X, A181E, S194X, and R202H) have been identified in exons 3 and 4 by sequence analysis of these two exons and the exon/intron boundaries.

Mutations in *TACI* have been found in about 20% of individuals with CVID in an American cohort and in 10% of a European cohort [Castigli et al 2005, Salzer et al 2005]. *TACI* mutations associated with CVID were also found in association with selective IgA deficiency [Castigli et al 2005, Salzer et al 2005]. An important caveat of these studies is that the observed incidence of *TACI* mutations in the American cohort almost certainly represents an upper limit on the real incidence of *TACI* mutations in simplex CVID (i.e., a single occurrence in a family), as many of the mutations found were present in families with clear evidence of autosomal dominant inheritance. Similarly, while the European cohort revealed ten individuals with TACI amino acid substitutions among 135 cases of simplex CVID, five of these individuals had a substitution, A181E, that was also found in a survey of normal controls. Thus, caution is warranted in regarding these studies as indicative of the actual incidence of *TACI* mutations in the most common simplex form of CVID and in drawing conclusions about the role of *TACI* A181E substitutions in the genesis of CVID in an individual.

ICOS encodes a T-cell immunoregulatory cell surface molecule, inducible co-stimulator, of the immunoglobulin superfamily that is expressed on activated T-cells.

A single large 1815 base pair deletion within the *ICOS* gene accounts for all *ICOS*-associated CVID reported to date [Grimbacher et al 2003, Salzer et al 2004]. Long-range PCR covering exons 2 and 3 detects the deletion in 100% of affected individuals [Salzer et al 2004]. Activated T-cells of individuals homozygous for this deletion lack ICOS protein expression.

This deletion has been found in fewer than 1% of individuals of European/American ancestry with CVID. The affected individuals are clustered geographically; three of four affected families live in the Black Forest region of Germany, and the other family lives in Lienz, Austria.

CD19 encodes a B-cell co-receptor molecule of the immunoglobulin receptor superfamily with a well established role in regulation of signaling through the B-cell antigen receptor. Mutations of *CD19* have recently been reported in association with CVID [Van Zelm et al 2006].

BAFFR encodes a B-cell immunoregulatory cell surface molecule of the TNF receptor superfamily, with an established role in regulation of peripheral B-cell homeostasis. Mutations of *BAFFR* have been reported in two families as preliminary data presented in an abstract [Warnatz, Salzer et al 2005].

Clinical Features—The specific molecular defect influences the type of immune dysregulation observed. Because current aggressive treatment of individuals with CVID with IVIG and antibiotics has markedly reduced the incidence of infections and other secondary sequelae, the underlying genetic defect is likely to be an increasingly important determinant of long-term outcome.

***TACI*-associated CVID** appears to be strongly associated with signs of lymphoproliferation, such as splenomegaly or tonsillar hypertrophy, which have been observed in 20-25% of

reported individuals. Autoimmune thyroiditis is observed in about 15% of reported individuals [Castigli et al 2005, Salzer et al 2005].

***ICOS* deficiency-associated CVID** has a classic CVID phenotype in the four families and nine affected individuals studied to date, with symptoms related to deficient humoral immune function, nodular lymphoid hyperplasia, autoimmunity, and susceptibility to malignancy [Warnatz, Bossaller et al 2005].

Unknown Causes

In 75-80% of individuals with CVID, the cause is unknown.

Evaluation Strategy

Once the diagnosis of CVID has been established in an individual, the following approach can be used to determine the specific cause of CVID to aid in discussions of prognosis and genetic counseling:

Family history

- Autosomal dominant inheritance suggests mutations in *TACI*.
- Autosomal recessive inheritance suggests mutations in *ICOS*, *BAFFR*, or *CD19*.
- X-linked inheritance suggests mutations in either *BTK* or *SH2D1A*.

Clinical examination

- Lymphoproliferative disease suggests mutations in either *SH2D1A* or *TACI*.
- Thyroiditis suggests mutations in *TACI*.

Testing

- Low B-cell numbers (which suggest mutations in either *BTK* or *SH2D1A*)
- Selective IgA deficiency (which suggests mutations in *TACI*)
- Loss of protein expression by cell type (Table 2)

Table 2. Loss of Protein Expression by Cell Type in Common Variable Immune Deficiency

Type of CVID	Cell Type	Absent Protein Expression [1]
TACI-associated	Peripheral B-cells	<5% of *TACI*-associated CVID
ICOS-associated	Activated T cells	100% of known
CD19-associated	Peripheral B-cells	100% of known
BAFFR-associated	Peripheral B-cells	100% of known

1. Includes detection rate for duplication/deletion testing

Molecular genetic testing. See Table 3.

Table 3. Molecular Genetic Testing Used in CVID

% of Individuals with CVID	Gene Symbol	Test Method	Mutation Detection Rate	Test Availability [1]
10-15%	*TNFRSF13B (TACI)*	Sequence analysis	100%	Clinical Testing
1% or less	*ICOS*		100%	
1% or less	*CD19*		100% of known	Research only
1% or less	*TNFRSF13C (BAFFR)*		100% of known	
75-80%	Unknown			

1. Per the GeneTests Laboratory Directory

Genetic Counseling

Genetic counseling is the process of providing individuals and families with information on the nature, 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. This section is not meant to address all personal, cultural, or ethical issues that individuals may face or to substitute for consultation with a genetics professional. To find a genetics or prenatal diagnosis clinic, see the GeneTests Clinic Directory.

Mode of Inheritance

The common variable immune deficiencies can be inherited in an autosomal dominant or autosomal recessive manner.

- *ICOS*-associated, *BAFFR*-associated, and *CD19*-associated CVID are inherited in an autosomal recessive manner.
- *TACI*-associated CVID is inherited in either an autosomal recessive or autosomal dominant manner, depending on the specific gene mutation involved and the penetrance of that allele in the affected family.

The cause and mode of inheritance are unknown in 75-80% of individuals with CVID.

If CVID is present in a male, or if a family exhibits an X-linked inheritance pattern, consideration should be given to exploration of mutations in the *BTK* or *SH2D1A* genes, as discussed in Differential Diagnosis.

Risk to Family Members — Autosomal Dominant Inheritance

Parents of a proband

- Some individuals diagnosed with autosomal dominant CVID will have an affected parent.
- A proband with autosomal dominant CVID may have the disorder as the result of a new gene mutation. The proportion of cases caused by de novo mutations is unknown.
- Because the degree to which an individual is affected by a given mutant allele and the timing of symptom onset (e.g., childhood vs. adulthood) may vary widely, unaffected parents may have subclinical CVID and/or the disease-associated allele identified in the proband.

- Depending on the mutant allele(s), the parents may be heterozygous or homozygous for a mutant allele, or may lack any mutant allele if the mutation in the proband is de novo.
- Homozygotes and heterozygotes are usually symptomatic, although the degree of penetrance of clinical symptoms may vary widely, depending on the gene mutation.

Sibs of a proband

- At conception, assuming that one parent has a disease-causing mutation, each sib of an affected individual has a 50% chance of inheriting the mutation and a 50% chance of not inheriting the mutation.
- If the disease-causing mutation found in the proband cannot be detected in the DNA of either parent, the risk to sibs is low, but greater than that of the general population, because the possibility of germline mosaicism exists.
- The degree to which an individual will be affected by a given allele and the timing of symptom onset (e.g., childhood vs. adulthood) may vary widely, such that testing or genetic evaluation should be considered for even apparently unaffected sibs.

Offspring of a proband

- Each child of an individual who is heterozygous for a mutation causing autosomal dominant CVID has a 50% chance of inheriting the mutation.
- The degree to which an individual will be affected by a given allele and the timing of symptom onset (e.g., childhood vs. adulthood) may vary widely, such that testing or genetic evaluation should be considered for even apparently unaffected offspring.

Other family members. The risk to other family members depends upon the status of the proband's parents. If a parent is found to have a disease-causing mutation, his or her family members are at risk.

As with sibs of a proband, since the degree to which an individual will be affected by a given allele and the timing of symptom onset (e.g. childhood vs. adulthood) may vary widely, testing or genetic evaluation should be considered for even apparently unaffected sibs of a proband's parents.

Risk to Family Members — Autosomal Recessive Inheritance

Parents of a proband

- The parents of an affected child are most likely obligate heterozygotes and therefore each carry one mutant allele.
- Heterozygotes (carriers) are usually asymptomatic.

Sibs of a proband

- At conception, each sib of an affected individual has a 25% chance of being affected, a 50% chance of being an asymptomatic carrier, and a 25% chance of being unaffected and not a carrier.
- Once an at-risk sib is known to be unaffected, the risk of his/her being a carrier is 2/3.
- Heterozygotes (carriers) are usually asymptomatic.

Offspring of a proband. The offspring of an individual with autosomal recessive CVID are obligate heterozygotes (carriers) for a disease-causing mutation.

Other family members. Sibs of the proband's parents are at 50% risk of being carriers.

Carrier Detection

- Carrier testing for family members at risk to be carriers of *TACI*-associated CVID or *ICOS*-associated CVID is available on a clinical basis once the mutations have been identified in the proband.
- Carrier testing using molecular genetic techniques for other mutations in other genes associated with CVID is not offered because it is not clinically available at this time.

Empiric Risks to Family Members

Counseling for individuals with CVID in whom the specific cause and/or mode of inheritance cannot be established (about 75-80%) is challenging.

Related Genetic Counseling Issues

Family planning. The optimal time for determination of genetic risk is before pregnancy.

DNA Banking. DNA banking is the storage of DNA (typically extracted from white blood cells) for possible future use. Because it is likely that testing methodology and our understanding of genes, mutations, and diseases will improve in the future, consideration should be given to banking DNA of affected individuals. DNA banking is particularly relevant in situations in which the sensitivity of currently available testing is less than 100% or testing is available on a research basis only for those families in which a molecular defect has not yet been established. See DNA Banking for a list of laboratories offering this service.

Prenatal Testing

Prenatal diagnosis for pregnancies at increased risk for *TACI*-associated or *ICOS*-associated CVID is possible by analysis of DNA extracted from fetal cells obtained by amniocentesis usually performed at about 15-18 weeks' gestation or chorionic villus sampling (CVS) at about 10-12 weeks' gestation. The disease-causing allele(s) of an affected family member must be identified before prenatal testing can be performed.

Note: Gestational age is expressed as menstrual weeks calculated either from the first day of the last normal menstrual period or by ultrasound measurements.

No laboratories offering molecular genetic testing for prenatal diagnosis of other types of CVID are listed in the GeneTests Laboratory Directory. However, prenatal testing may be available for families in which the disease-causing mutations have been identified in an affected family member. For laboratories offering custom prenatal testing, see Testing.

Preimplantation genetic diagnosis (PGD) may be available for families in which the disease-causing mutations have been identified in an affected family member. For laboratories offering PGD, see Testing.

Management

Evaluations at Initial Diagnosis to Establish the Extent of Disease

- **Hematologic.** Complete blood count, including white blood cell count and differential
- **Immunologic.** Serum concentration of IgM, IgG, IgA, IgE; lymphocyte subsets; T-cell immunophenotyping; B-cell immunophenotyping (including naove, non-

switched memory, and switched memory B-cells); lymphocyte proliferation to mitogens (PHA, anti-CD3, and specific antigens); appropriate molecular genetic studies; immunization with recall protein antigens (diphtheria, tetanus), polysaccharide antigens (pneumovax), and neoantigen (ΦX174)

Note: The neoantigen (ΦX174) test is a specialized test involving an investigational agent and local IRB permission.

Treatment of Manifestations

- **Humoral immune deficiency.** Immune globulin replacement therapy should be started as soon as possible to provide protective antibodies.
- **Infections.** Treat as appropriate with antibiotics.
- **Autoimmune phenomena.** Treat as appropriate for the manifestation.

In one series, it was noted that most episodes of autoimmune hemolytic disease occurred in those not yet on intravenous immune globulin therapy.

Prevention of Primary Manifestations

Administration of purified immune globulin is important in preventing the recurrent sinopulmonary infections associated with CVID. This can now be done via two routes: intravenously (i.e., IVIG) and subcutaneously.

- Generally, IVIG is dosed at 400 mg/kg every three to four weeks.
- Subcutaneous administration of immunoglobulin can be done with a variety of dosing schedules to suit the preference of a patient, with the overall goal of administering a total of 400 mg/kg every three to four weeks.

Prophylactic antibiotics may help prevent the recurrent sinopulmonary infections associated with CVID.

Antibiotics may help control small bowel bacterial overgrowth.

No therapies are known that will delay or prevent the onset of humoral immune deficiency associated with CVID.

Prevention of Secondary Complications

- **Chronic lung disease.** Recurrent sinopulmonary infections are a major contributor to the development of chronic lung disease; therefore, prophylaxis and treatment of these infections with IVIG and antibiotics are the most important means of preventing the progression of lung disease.
- **Autoimmune phenomena and malignancy.** No preventive measures are presently available.

Surveillance

- Periodic CBC and differential white blood cell (WBC) counts as lymphoma surveillance
- Annual thyroid examination as part of routine physical examination, with consideration of yearly thyroid function testing
- Annual pulmonary function testing beginning around age eight to ten years or when the child is capable of properly executing pulmonary function tests

- Every two or three years, high resolution CT scan to follow progression of lung disease
- Biopsy of any enlarged lymphoid tissue
- Consideration of other imaging modalities for assessment of progression of granulomatous disease and GI complications (CT, MRI, endoscopy, etc)

Agents/Circumstances to Avoid

Once IVIG therapy has begun, limiting contact of individuals with CVID from sick individuals is generally not needed.

For individuals with CVID and bronchiectasis, it is prudent to avoid contact with peat or other sources of aspergillus because of the capacity of aspergillus to colonize and establish difficult-to-eradicate and potentially invasive infections [Scharenberg et al, personal observation].

Testing of Relatives at Risk

Use of molecular genetic testing for early identification of at-risk family members may improve diagnostic certainty and so potentially reduce costly screening procedures in at-risk members who have not inherited disease-causing mutations. However, because several genetic causes of CVID are quite rare (e.g., *ICOS* deficiency, *BAFFR* deficiency, and *CD19* deficiency), testing is not clinically available for all genes, and the role of *TACI* in CVID is the subject of ongoing investigation, careful consideration of genetic testing is warranted on a case-by-case basis for each family.

Early recognition of clinical manifestations may allow timely intervention and improve outcome. Therefore, clinical surveillance of asymptomatic at-risk individuals for early detection is appropriate.

Therapies Under Investigation

In the next decade, one or more forms of gene therapy or gene repair that are sufficiently safe to be applied to the prevention of CVID may be developed.

Search ClinicalTrials.gov for access to information on clinical studies for a wide range of diseases and conditions.

Resources

GeneReviews provides information about selected national organizations and resources for the benefit of the reader. GeneReviews is not responsible for information provided by other organizations. Information that appears in the Resources section of a GeneReview is current as of initial posting or most recent update of the GeneReview. Search GeneTests*for this disorder and select* Resources *for the most up-to-date Resources information.*—ED.

Immune Deficiency Foundation
40 W Chesapeake Ave Suite 308
Towson MD 21204
Phone: 800-296-4433; 410-321-6647
Fax: 410-321-9165
Email: idf@primaryimmune.org
www.primaryimmune.org

International Patient Organisation for Patients with Primary Immunodeficiencies
Firside Main Road

Downderry
Cornwall PL11 3LE
United Kingdom
Email: david@pia.org.uk
http://ipopi.org/

Jeffrey Modell Foundation/National Primary Immunodeficiency Resource Center
747 Third Avenue 34A
New York NY 10017
Phone: 800-533-3844; 212-819-0200
Fax: 212-764-4180
Email: info@jmfworld.org
www.info4pi.org

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Medical Genetic Searches: A specialized PubMed search designed for clinicians that is located on the PubMed Clinical Queries page. PubMed

Published Statements and Policies Regarding Genetic Testing

No specific guidelines regarding genetic testing for this disorder have been developed.

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