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Review

Birds of a feather

Common variable immune deficiencies

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Key Messages

- Common variable immune deficiency (CVID) is suggested by a clinical phenotype of infectious susceptibility, autoimmunity, and lymphoproliferation. A diagnosis is made with laboratory evidence of antibody failure.
- Genetic variants likely contributing to CVID can be identified in up to 30% of patients.
- Genetic mutations are enriched in patients with CVID with any of the following: early-onset manifestations, autoimmune or inflammatory complications, a family history of immunodeficiency, or low B-cell numbers.
- Identification of a mutation in a CVID-related gene can have direct prognostic and therapeutic implications.

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ABSTRACT

Objective: To update the reader on recently proposed common variable immune deficiency (CVID) diagnostic criteria, newly uncovered CVID pathobiology, freshly identified CVID-related genes, and novel CVID therapies.
Data Sources: PubMed Central.
Study Selections: We selected 60 clinical and translational research articles that have shaped CVID diagnostic criteria, introduced personalized therapies, and advanced our understanding of CVID biology and genetics. We have incorporated recent articles and older published work that are foundational to the modern understanding of this protean disease.
Results: CVID has proven to be a heterogenous group of antibody deficiency diseases driven by defects in diverse biologic processes, including B-cell development, activation, tolerance, class-switch recombination, somatic hypermutation, and lymphoproliferation. Recent genetic advances have enabled identification of several CVID-related gene defects that may contribute to patients' infectious and noninfectious symptoms.
Conclusion: Improved understanding of the aberrant biologic processes that drive CVID and the disease's genetic basis may be useful in directing therapeutic decisions, especially in cases complicated by autoimmune, lymphoproliferative, and inflammatory features.
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Introduction

As implied by its name, common variable immunodeficiency (CVID) is the most prevalent symptomatic primary immunodeficiency in adults and is a diagnosis frequently considered by the practicing allergist and clinical immunologist. Despite practitioner familiarity, there is disagreement about which immune deficient patients should be diagnosed as having CVID. As the name also implies, patients with CVID often exhibit protean clinical manifestations.[1,2] Reflecting this, the International Union of Immunological Societies Classification of Primary Immunodeficiency refers to CVID as a *group* of disorders with several clinical and laboratory phenotypes rather than a single disorder.[3] In recent years, an

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Table 1
Disease Features Enriched in Monogenic CVID

Lymphoproliferative disease (lymphadenopathy, splenomegaly and/or granulomatous lymphoinfiltrative lung disease)
Autoimmune disease
B-cell lymphopenia
CVID-affected blood relations

Abbreviation: CVID, common variable immune deficiency.

increasing number of CVID-associated genetic defects have been identified (so-called monogenic CVID). Awareness of these mendelian disorders is important for the practitioner because establishing a genetic basis of a patient's disease can have significant implications for prognosis (eg, risk of autoimmune disorders, lymphoproliferation, or malignant tumor), treatment (eg, with targeted therapies), and family planning. Conversely, because possible genetic contributors can be identified for at most 30% of patients with CVID[4,5] based on currently available information and many genetic forms of CVID exhibit incomplete penetrance, the approach of screening *all* patients with CVID for a genetic cause is low yield. Thus, of equal importance for practitioners is awareness of the key clinical and immunophenotypic features of monogenic CVID (Table 1), which indicate the patients most likely to benefit from genetic testing.

Diagnosis and Diagnostic Criteria

Multiple diagnostic criteria have been proposed for CVID, all of which differ slightly (Table 2).[6–9] Unifying the assorted criteria are laboratory evidence of antibody failure (hypogammaglobulinemia and absent plasma cells in gut biopsy specimens), impaired class switching (reduced class-switched memory B-cell formation), and poor specific antibody responses to natural antigens and/or vaccines. There are several distinguishing nuisances between criteria that we wish to highlight. First, both the European Society for Immunodeficiencies (ESID) 2014 and International Consensus Document (ICON) 2015 criteria do not require patients with CVID to be symptomatic as long as they meet laboratory diagnostic criteria, particularly if there is a family history of immunodeficiency. Although treating asymptomatic people with immunoglobulin

Table 2
Comparison of Published Diagnostic Criteria for CVID

Variable	ICON,[7] 2015	ESID,[9] 2014	Ameratunga et al,[6] 2013[a]	ESID/PAGID,[8] 1999
Clinical features	At least one of the following: infection, autoimmunity, lymphoproliferation; can diagnose even if asymptomatic (especially if family history of CVID) but must fulfill all other criteria	At least one of the following: infection, autoimmunity, granulomatous disease, unexplained polyclonal lymphoproliferation, affected family member with antibody deficiency	Must have symptoms of increased susceptibility to infections, autoimmunity, and inflammatory disorders (Category B)	
Age	Not specified	>4 years for diagnosis	>4 years for diagnosis (Category A)	Onset at ≥2 years
Immunoglobulins	Low IgG level on at least 2 measurements taken >3 weeks apart (repeat measurement not needed if IgG very low); IgA and/or IgM levels must also be low	Low IgG and low IgA levels with or without low IgM level, measured at least twice	IgG <500 mg/dL (for adults) (Category A). Low IgA, low IgM, and low IgG3 levels each are 1 point in Category C (but none is required)	Low IgG level; IgA and/or IgM levels must also be low
Antibody response	Impairment of response to antigens compared with healthy controls (can skip if IgG level is <100 mg/dL)	Poor response to vaccines (nonprotective titers) and/or absent isohemagglutinins OR low (<70% age-matched controls) switched memory B cells	Absent isohemagglutinins and impaired or short-lived vaccine response compared with healthy controls each are 1 point in Category C (but neither is required)	Absent isohemagglutinins and/or poor response to vaccines (nonprotective titers)
Other laboratory criteria	None defined	No profound T-cell deficiency	Low memory B cells/increased CD21, low B cells, and serologic evidence of significant autoimmunity each are 1 point in Category C (but none is required)	
Genetic criteria	Genetic testing should be considered for patients with immune dysregulation, autoimmunity, malignant tumor, or other complications	None defined	Sequence variation in gene predisposing to CVID is not required (if present, 1 point in Category C); if pathogenic change found in gene causing monogenic CVID-like disorder found, patient is no longer considered to have CVID	
Histologic criteria	None defined	None defined	Absent plasma cells on gut biopsy, nodular regenerative hyperplasia of liver, nodular lymphoid hyperplasia of gut, sarcoid-like granulomatous disorder, and/or lymphocytic interstitial pneumonitis (Category D)	
Other criteria	Exclude secondary causes of hypogammaglobulinemia	Exclude secondary causes of hypogammaglobulinemia	Exclude secondary causes of hypogammaglobulinemia (Category A)	Exclude secondary causes of hypogammaglobulinemia

Abbreviations: CVID, common variable immune deficiency; ESID, European Society for Immunodeficiencies; ICON, International Consensus Document; PAGID, Pan-American Group for Immunodeficiency.
[a]Must meet all Category A and B requirements AND have 3 points for Category C OR meet Category D.

Table 3
Biologic Effects of CVID-Associated Gene Defects

Biologic defect	CVID-associated genes
Impaired B-cell development and survival	*IKZF1, BAFFR, TWEAK, NFKB2, CD27, IRF2BP2, STAT1 GOF*
Impaired class switch recombination/ somatic hypermutation	*BACH2, IL21, IL21R*
Excessive lymphoproliferation	*CTLA4, LRBA, PIK3CD, PIK3R1, STAT3 GOF*
Impaired B-cell activation and tolerance	*NFKB1, TACI, CD19, CD21, CD81, CD20, ICOS, BLK, PLCG2*

Abbreviation: CVID, common variable immune deficiency.

replacement therapy could hypothetically prevent future infections, this approach is controversial because it exposes overtly healthy populations to adverse infusion risks and is arguably wasteful of limited medical resources.[10] Although a scoring system to help guide clinical decision making on when to initiate treatment has been proposed, data are lacking on the long-term outcomes of these patients to support treatment vs watchful waiting.[11,12] Therefore, efforts to diagnose asymptomatic patients with CVID, although potentially useful for research study enrollment, may not lead to clinically meaningful outcomes.

Second, we emphasize restraint in diagnosing patients whose IgG and/or IgA and IgM levels fall just outside the reference range with CVID. Serum immunoglobulin levels vary significantly between healthy humans and may fluctuate over time. Thus, if the history is not concerning and the practitioner deems it reasonable to observe the patient for a longer period, it is reasonable to remeasure serum antibody concentrations after a reasonable interval to determine whether a patient's antibody deficiency has resolved or progressed.[12] We would also stress the importance of performing vaccine challenges in evaluating patients with borderline serum antibody concentrations because it is poor antibody quality, not lower antibody quantity, that is the best predictor of infectious susceptibility.

Third, we emphasize the utility of measuring serum IgE in patients with suspected CVID because a high serum IgE level is uncommon in patients with CVID and should suggest alternative diagnoses. An undetectable serum IgE level is much more common in patients with CVID than in the healthy population.[13]

General Biologic Processes That Drive CVID Pathologic Processes

Because CVID causes are diverse, complex, and often unclear, an appreciation of the biologic processes that drive these disorders can aid in the diagnosis and treatment of complex cases. Paramount in CVID pathogenesis is B-cell dysfunction, including defects in development and survival, class-switch recombination (CSR), and somatic hypermutation (SHM), activation, and tolerance (Table 3). Other factors that influence the CVID immune system are lymphoproliferative processes that are cell intrinsic or secondary to endotoxemia,[14] cytokine dysregulation,[15,16] or viral infections.[17]

Although most patients with CVID have preserved peripheral B-cell numbers, a rarer CVID phenotype is B-cell lymphopenia. Defects in pathways that are involved in early bone marrow–dependent B-cell development, including heavy and light chain rearrangements and expression of surface IgM, result in absent peripheral B cells and agammaglobulinemia. The most well-recognized form of this is X-linked agammaglobulinemia, which is caused by mutated Bruton tyrosine kinase, a protein essential for pre–B cells to transition to immature B cells in the bone marrow (Fig 1).[18] In addition, several forms of autosomal recessive and autosomal dominant congenital agammaglobulinemia have been recently described, which can affect both males and females[18] and are generally considered separately from CVID. Excluding patients with these early B-cell development defects, up to 20% of patients with CVID in large published cohorts have severe peripheral B-cell deficiency. Bone marrow examination of these patients may exhibit partial arrest of B-cell development at the pre–B-cell stage resembling hypomorphic congenital agammaglobulinemia.[19] In some patients with CVID, B-cell lymphopenia is a durable feature; in others, B-cell loss may be insidiously progressive.

A B cell interrogates its surroundings with its antigen-specific B-cell receptor (BCR) and germline-encoded pathogen associated molecular pattern receptors, including Toll-like receptors (TLRs) 7 and 9. On detecting a cognate antigen or any number of pathogen associated molecular patterns, a circulating healthy donor B cell becomes activated, proliferates, and homes to a lymphoid follicle. There, it is coactivated, expresses activation-induced cytidine deaminase (AID), performs CSR, undergoes SHM, and

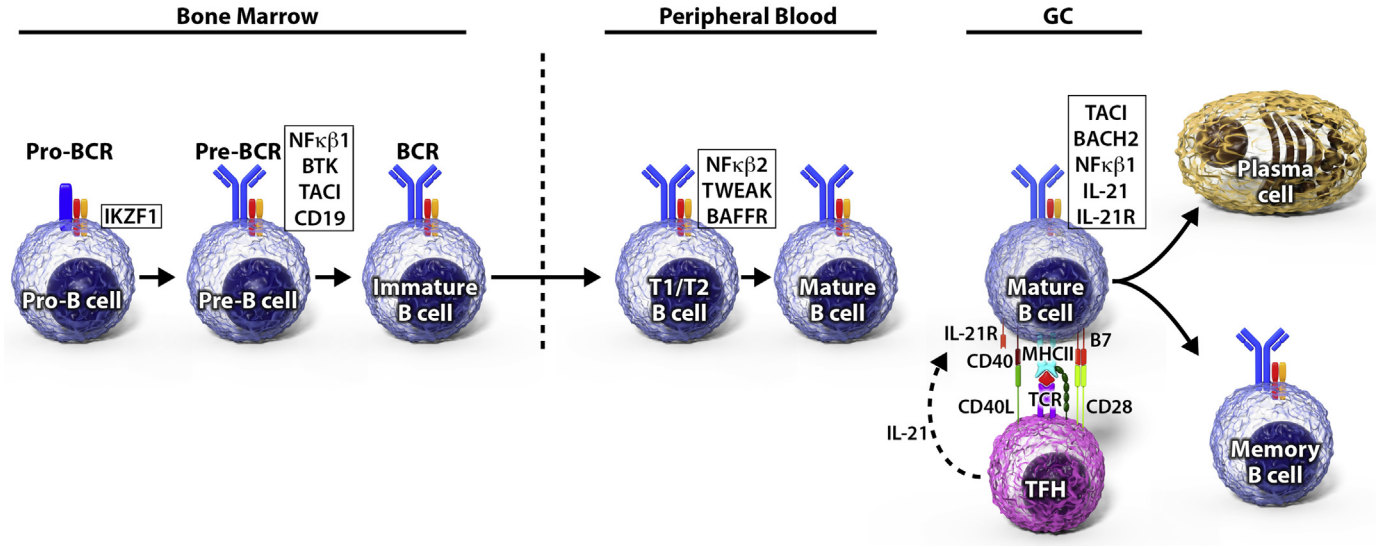

Figure 1. Common variable immune deficiency–associated gene defects (boxed) affect B-cells at distinct developmental stages. BAFF-R, B-cell activating factor receptor; BCR, B-cell receptor; GC, germinal center; IL-21, interleukin 21; IL-21R, interleukin 21 receptor; MHC, major histocompatibility complex; TCR, T-cell receptor; TFH, T follicular helper (cells).

differentiates into a long-lived plasma cell (Fig 1). Defective CSR and SHM are central features of CVID long included in clinical diagnostic criteria. Uracil N-glycosylase and AID mediate CSR and SHM in germinal center B cells, permitting generation of high-affinity IgG and IgA for secretion or cell surface expression by class-switched (IgM^-) memory ($CD27^+$) B cells. Because mature B cells from most patients with CVID are less responsive to BCR and TLR ligation, it is not surprising that these patients fail to produce high-affinity, class-switched antibodies when challenged with vaccines or natural infections.[20,21] For most CVID cases, CSR and SHM dysfunction are also likely attributable to 1 or more CVID-related B-cell intrinsic activation defects,[15,21] but because coactivation is also important for AID expression, T-cell intrinsic defects can be contributory. Unable to class switch, a proportion of the CVID population exhibits normal or increased serum IgM concentrations. Once blood dyscrasias have been excluded via laboratory testing, it may be conceptually useful to consider patients with IgM-overproducing CVID as phenotypically similar to AID-deficient patients with hyper-IgM syndrome. Indeed, follicular hyperplasia and autoimmune cytopenias feature prominently in each group.[14,22]

Recent recognition of the critical roles BCR and TLR perform in counterselecting autoreactive B-cell clones has led to the realization that B-cell tolerance defects are central features of CVID.[14,15] Breeched tolerance may explain the high prevalence of autoantibody-mediated diseases in patients with CVID, a feature now included in multiple recent diagnostic criteria (Table 2).[23] Autoantibody production in an antibody-deficient patient may seem paradoxical but is consistent with the tolerogenic roles BCR and TLR play in early B-cell development. At completion of V(D)J recombination, most early immature B cells are autoreactive and must be purged while still developing in the bone marrow.[24] Because BCRs and TLRs are essential for the identification and counterselection of self-reactive developing B cells, CVID-associated BCR and TLR defects permit autoreactive CVID B cells to escape counterselection during development.[15] Additional, more peripheral tolerogenic mechanisms, such as clonal redemption, which involves SHM away from self-peptide recognition, are also compromised in the B cells of patients with CVID.[14,25]

One of the most clinically challenging features of CVID is lymphoproliferation, a process that can injure multiple organs, including bowel (enterocolitis), lung (granulomatous and lymphocytic interstitial lung disease), and brain.[1] No matter the anatomical site, these pathologic processes stem from excess signals promoting cellular division or the lack of regulatory mechanisms restraining it. In some cases, the causes of lymphoproliferation are cell intrinsic, whereas in others they are secondary to CVID-associated inflammation. For instance, patients with starkly IgA-deficient CVID appear endotoxemic, which is highly associated with lymphadenopathy, florid follicular hyperplasia, and accumulation of highly proliferated, exhausted $CD21^-$ B cells.[14,26] In other cases, primary or reactive lymphoproliferation appears to transform into malignant cell division. The risk of cancer in patients with CVID, especially of non-Hodgkin and Hodgkin lymphoma, is significantly increased.[23]

Specific Monogenic Defects Associated With CVID

Defects in B-Cell Development

Early defects in bone marrow B-cell development result in congenital agammaglobulinemia. CVID B cells, in contrast, may arrest after marrow egress into the periphery but before maturation, selectively lack the ability to terminally differentiate into antibody-producing plasma cells, or have impaired survival.[27] Survival of B cells in the periphery requires the interaction of B-cell activating factor (BAFF) and B-cell activating factor receptor (BAFF-R), an interaction that is most critical for transitional B-cell differentiation into marginal zone and follicular B cells in the spleen.[28] BAFF-R–deficient patients can be recognized by B-cell lymphopenia, relatively increased transitional B-cell frequencies caused by maturational arrest, and preserved levels of serum IgA (which is in direct contrast to most patients with CVID, who have reduced IgA levels).[29] Similarly, mutations of *TWEAK* and *NFKB2*, which both encode signalling molecules downstream of BAFF-R, cause hypogammaglobulinemia and markedly reduced peripheral B cells with impaired formation of memory B cells.[30,31] B cells from patients with monogenic CVID may also exhibit normal maturation but impaired survival. One example is patients with heterozygous mutations in *IKZF1*, the gene encoding for the hematopoetic transcription factor IKAROS.[32] IKAROS-haploinsufficient patients present at any age with recurrent/severe bacterial infections as well as autoimmunity, including idiopathic thrombocytopenic purpura and systemic lupus erythematosus.[33] A unique and defining characteristic of this particular form of CVID is the progressive loss of immunoglobulins and peripheral B cells with age, a feature thought to be caused by premature stem cell senescence. Patients with *IKFZF1* mutations can be distinguished from other forms of CVID by the presence of some $CD27^+$ memory B cells and plasma cells, which are thought to have been generated earlier in life before commencement of accelerated B-cell death. Most patients with CVID have markedly reduced numbers of switched memory B cells and low or absent plasma cells.[34]

Defects in CSR and SHM

Although most patients with defects in CSR or SHM have elevated IgM levels and are classified as having a hyper-IgM syndrome, defects in CSR and SHM are also found in certain monogenic forms of CVID. Interactions of interleukin (IL) 21 with its receptor are critical for multiple immune pathways and therefore as predicted mutations in either protein have pleiotropic effects. Focusing on those related to CSR and SHM, the addition of IL-21 along with costimulatory molecules has been shown to induce the expression of AID, regulating the CSR of naïve B cells to IgG and IgA.[35] Not surprisingly, then, patients with IL-21 and IL-21 receptor (IL-21R) deficiency present with a CVID-like illness that is distinguished by markedly elevated levels of serum IgE (by pathways that are still not well defined), a characteristic that is uncommon in most patients with CVID.[13,36] In addition, patients with IL-21R deficiency have a unique susceptibility to *Cryptosporidium* infections along with other opportunistic infections, whereas patients with IL-21 deficiency have very early-onset inflammatory bowel disease.[36,37] In vitro studies have demonstrated a failure of naïve B cells from patients with IL-21R deficiency to undergo class switch in response to stimulation, along with impaired upregulation of AID and B-lymphocyte–induced maturation protein 1.[36] Although hematopoietic stem cell transplant is a potential therapeutic option for these patients, this has met with limited success clinically, perhaps because of underlying comorbidities at the time of transplant.[36]

BACH2 is a transcription factor that promotes AID expression, allowing CSR to occur.[38] It is also involved in controlling effector T-cell differentiation and senescence and permitting the formation of regulatory T cells. Patients with mutations in *BACH2* have low IgG, IgA, and IgE levels and impaired response to vaccines as would be predicted, but surprisingly an elevated serum IgM level is not consistently seen.[39] In vitro, B cells have impaired CSR in response to IL-21 and reduced plasmablast generation, as well as a skewing toward T_H1 immunity with impaired regulatory T-cell formation. This latter feature likely underlies an early-onset autoimmune inflammatory bowel disease.

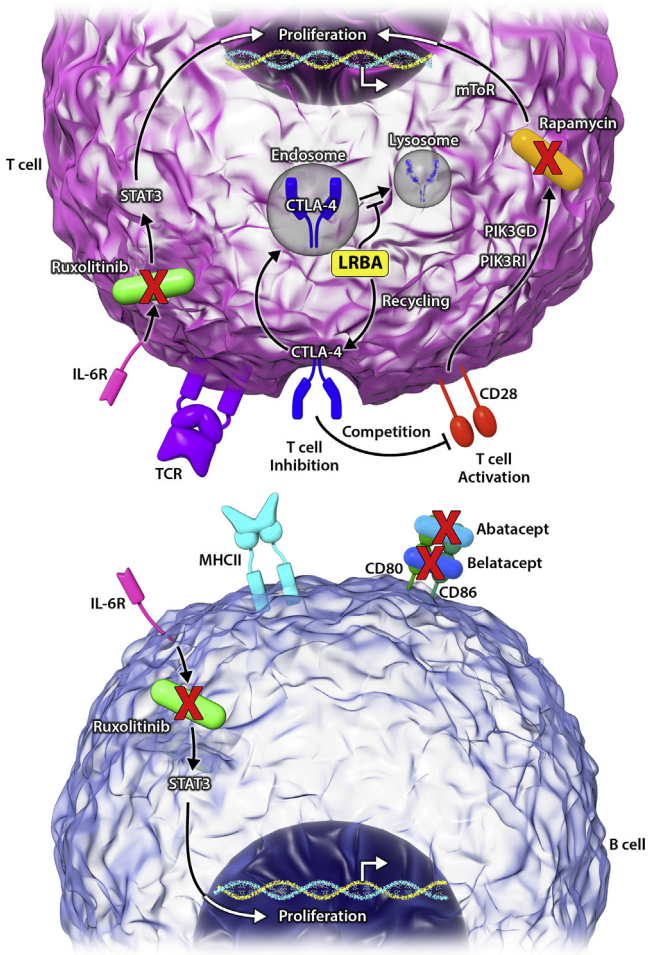

Figure 2. Interleukin 6 (IL-6) and coactivation promote T-cell proliferation. T-cell coactivation is regulated by competition by cytotoxic T-lymphocyte–associated protein 4 (CTLA4) for CD80/86. Druggable targets are indicated with red crosses. LRBA, lipopolysaccharide-responsive beige-like anchor protein; MHC, major histocompatibility complex; mTOR, target of rapamycin; TCR, T-cell receptor.

B-Cell Activation and Central Tolerance Defects

Many monogenic forms of CVID are caused by defects in BCR and/or TLR signaling pathways. For instance, deficiencies of any of the components of the B-cell coreceptor complex (CD19/CD21/CD81),[40–42] the signaling proteins it recruits (BLK/PLCG2), or influencers of downstream calcium flux (CD20) limit BCR-mediated activation. Negatively affecting both BCR and TLR pathways are CVID-associated mutations of genes encoding *TACI, NFKB1*, and *CD19*.[15,40,43–45] A significant proportion of patients with CVID with molecular defects affecting BCR and TLR signaling experience autoantibody-mediated disorders. For instance, 40% to 50% of patients with CVID with heterozygous *TACI* or *NFKB1* mutations experience autoimmune cytopenias during their disease.[46,47] Although highly effective in the near term, the durability of B-cell depletion in patients with CVID with central B-cell tolerance defects is limited. Autoreactive B cells repopulate the niche on immune reconstitution, although in some cases B-cell development occurs slowly or not at all for unclear reasons.

Lymphoproliferative Defects

Monogenic lymphoproliferative CVID may be functionally categorized into 2 groups. Driving pathology in one group are gain-of-function mutations in genes that drive cellular division, including *PIK3CD, PIK3R1* and *STAT3*. Driving pathology in the other group are loss-of-function mutations in regulatory genes restraining cell division such as *CTLA4* and *LRBA*. Notably, within this group of patients, some, but not all, will present with the classical laboratory features of CVID.

Patients with heterozygous-activating mutations in *PIK3CD* or *PIK3R1* (APDS), alternatively named p110δ-activating mutation causing senescent T cells, lymphadenopathy and immunodeficiency, present heterogeneously.[48,49] It may seem counterintuitive, but the same proliferative biology that skews APDS lymphocytes toward terminally differentiated effector phenotypes also renders them too exhausted to respond to many pathogens.[50] Because PIK3CD and PIK3R1 are critical to BCR and T-cell receptor signaling, it is not surprising that patients with APDS are susceptible to both recurrent infections with encapsulated organisms (*Streptococcus pneumoniae* and *Haemophilus influenzae*) and severe, recurrent herpes family virus infections (Epstein-Barr virus, cytomegalovirus, herpes simplex virus, and varicella-zoster virus). When these organisms infect the respiratory tract, patients with APDS are more likely to have progressive airway damage (bronchiectasis and mosaic attenuation on imaging) than other patients with CVID.[48] In addition to infections, one-third of patients with APDS exhibit autoimmune diseases, primarily autoimmune cytopenias. Most exhibit nonmalignant lymphoproliferative diseases, including lymphadenopathy, hepatosplenomegaly, and focal nodular lymphoid hyperplasia. There is an increased risk of lymphoma.[51] The antiproliferative drug rapamycin has been successful in normalizing the T-cell profiles of patients with APDS and their lymphoproliferative symptoms.[52]

Similar to gain-of-function *PI3KCD* mutations, patients with heterozygous gain-of-function *STAT3* mutations typically present with hypogammaglobulinemia, infectious symptoms, and a panoply of autoimmune manifestations, including type 1 diabetes, autoimmune cytopenias, nonmalignant lymphoproliferation, and enteropathy.[53–55] Unlike loss-of-function *STAT3* mutations, which cause mucocutaneous candidiasis, *STAT3* gain-of-function mutations can present with disseminated nontuberculous mycobacteriosis.[54] Because STAT3 serves the IL-6 receptor, it is not surprising that tocilizumab has some efficacy in treating the autoimmune manifestations of patients with STAT3 gain of function[53] (Fig 2). There may be additional benefit to adding a jakinib, such as ruxolitinib, in patients with disease resistant to tocilizumab monotherapy.[56]

Cytotoxic T-lymphocyte–associated protein 4 (CTLA4) regulates T-cell proliferation by tempering T-cell receptor signal strength and by outcompeting CD28 for coactivating B7 ligands (Fig 2). Heterozygous loss of CTLA4 in humans causes autoimmune lymphoproliferative syndrome type 5 (ALPS5).[57,58] The central features of ALPS5 are autoimmune cytopenias and lymphoinfiltrative damage to organs such as the bowel and brain. Lipopolysaccharide-responsive beige-like anchor protein (LRBA) is cytoskeletal protein that is essential for maintaining intracellular stores of CTLA4 through recycling. Accordingly, LRBA-deficient T cells behave similarly to CTLA4-haploinsufficient T cells, causing similar autoimmune features in affected patients.[59,60] Although only a quarter of patients with ALPS5 meet CVID criteria,[61] more than half of LRBA-deficient patients are hypogammaglobulinemic.[62] It is unknown whether the antibody deficiency encountered in either disease is primary or secondary to the polypharmacy required to control these patients' autoimmune disease(s). CTLA4 immunoglobulin (abatacept or belatacept) has proven to be an effective and well-tolerated personalized therapy in LRBA deficiency and CTLA4-haploinsufficient patients.[60,63]

Conclusion

Currently, variants in single disease-associated genes can be identified in as many as 30% of patients who meet the CVID clinical

criteria.[4,5] As the number of gene defects linked to CVID continues to increase, it is becoming increasingly challenging for practitioners and researchers to remain knowledgeable. Therefore, it is arguably more important to develop a conceptual framework around the molecular pathways and general biologic processes defined above that could lead to CVID. Performing a careful clinical and immunophenotypic evaluation of the patient to look for clues as to the underlying cause (eg, the presence of autoimmunity/impaired tolerance, lymphoproliferation, or reduced B-cell numbers implying impaired B-cell survival) may assist physicians in selecting patients most likely to benefit from genetic testing (Table 1). Identification of a damaging mutation in a CVID-associated gene can provide important clues into prognosis and potentially suggest targeted treatment strategies. Current challenges to the genetic evaluation of patients with CVID include insurance reimbursement and the availability of reliable functional tests to validate gene variants of unknown significance. To more completely understand the disease, future investigations must grapple with the theoretic likelihood that mutations in more than one gene, noninherited somatic mutations, and nongenetic, environmental factors all contribute to an unknown but potentially large proportion of CVID cases.

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