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ORIGINAL ARTICLE

# Autoimmunity and Inflammation in CVID: a Possible Crosstalk between Immune Activation, Gut Microbiota, and Epigenetic Modifications

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## Abstract

Common variable immunodeficiency (CVID) is the most common symptomatic primary immunodeficiency among adults and is characterized by a B cell dysfunction and increased risk of respiratory tract infections with encapsulated bacteria. However, a large proportion of patients also has inflammatory and autoimmune complications. It may seem like a paradox that immunodeficiency and inflammation/autoimmunity coexist within the same individuals. In this commentary, we propose that CVID immunopathogenesis involves an interplay of genes, environmental factors, and dysregulation of immune cells, where gut microbiota and gastrointestinal inflammation can both be important contributors or endpoints to the systemic immune activation seen in CVID, and where epigenetic mechanism may be the undiscovered link between these contributors. In our opinion, these pathways could represent novel targets for therapy in CVID directed against autoimmune and inflammatory manifestations that represent the most severe complications in these patients. Considering the heterogeneous nature of CVID, these mechanisms may not be present in all patients, and different complications may be triggered by different risk factors. CVID is really a variable disease and in the future there is clearly a need for a more personalized medicine based on both genotypic and phenotypic findings.

**Keywords** Common variable immunodeficiency · autoimmunity · inflammation · mucosal immunology · gut microbiota epigenetic · Primary immunodeficinecy

## Common Variable Immunodeficiency: More than Immunodeficiency

Common variable immunodeficiency (CVID) is the most common symptomatic primary immunodeficiency among adults with a prevalence of 1:25 000 to 1:50 0000 in Caucasians [1]. The disease is characterized by a B cell dysfunction resulting in hypogammaglobulinemia and respiratory tract infections with encapsulated bacteria. However, in spite of their immunodeficiency, a large proportion of patients have inflammatory and/or autoimmune complications referred to as non-infectious complications [2, 3]. In a study by Chapel *et al.* ($n = 334$), 74% of CVID patients had non-infectious complications of which 42% of CVID patients had autoimmune disorders, and in a study by Resnick *et al.*, ($n = 473$) 68% of CVID patients had non-infectious complications of which 29% of CVID patients had autoimmune disease. In these two studies, inflammatory complications, not included in the group of specific autoimmune disorders, comprised polyclonal lymphocyte infiltration (e.g., splenomegaly, persistent lymphadenopathy, unexplained granuloma, unexplained hepatomegaly, and lymphoid interstitial pneumonitis), gastrointestinal (GI) inflammation, and malignancies [2, 3]. In a very recent study by Fischer *et al.*, performed in a large population of patients with primary immunodeficiency ($n = 2183$), the frequency of autoimmune disorders was 26%. They also showed that the greatest risk for these manifestations was in patients with T cell deficiencies (27.5%) and CVID (38.3%) [4]. The heterogeneity seen in CVID patients with regard to the reported non-

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infectious complications between the different study sites may be due to the difference in diagnostic protocols and clinical assessment as well as differences in the definition of these complications, as previously discussed [5]. For example, the prevalence of splenomegaly and lymphoid hyperplasia will be higher at centers routinely performing CT scans/endoscopies (lymphoid hyperplasia in the GI tract) of all patients during follow-up. In addition, an underlying geographic/population effect due to genetic background may also exist. Importantly, however, both the recent study by Fischer et al. as well as previous CVID studies [3] show that survival was reduced in CVID patients with autoimmune and inflammatory complications. It is therefore of major importance to elucidate mechanisms that lead to these non-infectious complications also from a therapeutic point of view.

## CVID: a Heterogeneous Group of Disorders

There is no universally accepted definition of CVID, but a minimum criterion is decreased IgG with reduced IgA and/or IgM with the exclusion of other secondary causes of hypogammaglobulinemia [6], and may include poor antibody response to vaccines as diagnostic criteria [7]. Recently, however, ESID has suggested new working diagnostic criteria where vaccine response is no longer an absolute criterion, and while certain clinical characteristics including autoimmunity and certain B cell phenotypes are included as diagnostic criteria, patients with evidence of profound T cell deficiency are excluded from the CVID definition [8]. Thus, although CVID may consist of several defined small subgroups based on genetic and phenotypic characteristics [7], the term CVID may still be useful from a clinical point of view.

The monogenic defects associated with a CVID phenotype have been rapidly expanding and estimated to be as high as 10–25% in some cohorts and suggest that CVID consists of several different diseases with different pathophysiological mechanisms. However, the exact proportion of monogenic cases in CVID is dependent on referral practice and genetic background of the cohort screened. Irrespective of the actual number, a large percentage of patients remains genetically uncharacterized in terms of monogenic defects. There are some observations supporting that for a considerable proportion of CVID patients, the inheritance is more consistent with a complex pattern of inheritance. For example, in a large genetic association study in 778 CVID patients from five countries, we found that *CLEC16A* was a susceptibility gene for CVID, which is also found as a risk gene in many autoimmune diseases, suggesting a genetic overlap between CVID and autoimmunity [9]. However, much larger cohorts are often needed to detect numerous GWAS significant susceptibility genes, and with a rare disease like CVID it is difficult to bring together large enough cohorts to detect a significant polygenic disease risk profile. Nevertheless, even for more common complex genetic diseases, a substantial fraction of the heritability remains unexplained and only the top of the iceberg is detected [10].

As of today, it seems that the heterogeneous phenotype that makes up the CVID diagnosis includes a combination of a smaller proportion of patients with monogenic diseases and a larger proportion of patients with complex genetic inheritance involving multiple genetic and environmental factors (Fig. 1). Although the proportion of patients with the potential monogenic disease most probably will increase during the coming years owing to the improvement in methodology and knowledge, the phenotypes in those with monogenic CVID disease seems to vary. This suggests that even in these patients, other genetic, including epigenetic, modifications and environmental factors may be involved. Although many patients experience symptoms in the first decade of life, with a peak of incidence in early adulthood, the debut can be at any age and as late as 60–70 years of age. This could further point towards an environmental trigger in genetically susceptible individuals (Fig. 1). However, although particularly infectious triggers have been investigated, no environmental risk factors have so far been identified in CVID, whereas epigenetic mechanisms have scarcely been studied. Moreover, the reason why some patients suffer from infections only while others develop autoimmune

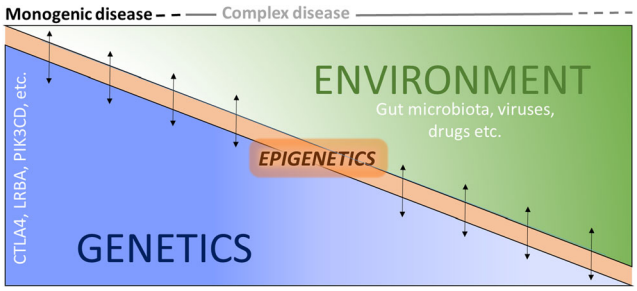


**Fig. 1 The spectrum of contribution by environmental factors and genetics in immunodeficiency conditions and the possible role of epigenetics.** At one end are the familial monogenic conditions with little influence from the environment, and at the other end are the environmental factors, e.g., certain drugs that lead to the development of hypogammaglobulinemia without seemingly being much influenced by genetics. A fraction of CVID patients are likely monogenic disease (10–25%), left side of figure, whereas the remainder of the CVID patients is likely a result of complex genetic inheritance (complex disease) with a polygenic risk profile and unknown environmental factors required for disease development, middle section of the figure. Particularly for complex disease, epigenetic mechanisms, "turning genes on and off," may be the missing link between environmental triggers and a genetic risk profile, influencing penetrance of disease. However, even monogenic disease may be influenced by epigenetics, potentially offering an explanation for the incomplete penetrance and diverge phenotypes seen in e.g., *LRBA*, *CTLA4*, and *PIK3CD*. In addition, monogenic diseases could also be influenced by gene-gene interaction making the strict division into monogenic and complex disease somewhat overlapping (black dotted line). Likewise, even in environmental induced immunodeficiency, e.g., treatment with rituximab and certain anti-epileptic drugs, genetic susceptibility and epigenetics mechanisms could potentially influence disease phenotype, e.g., who develops hypogammaglobulinemia (gray dotted lines)

and inflammatory complications is still elusive but may involve both genetic and environmental factors.

Previously, dysregulation of B cells, T cells, and macrophages has been linked to an inflammatory and autoimmune phenotype in CVID (Fig. 2), although the underlying mechanisms are not clear. In this commentary, we suggest that the interactions between gut microbiota and the immune system, with epigenetic modifications as the possible missing link, could play a pathogenic role, at least in subgroups of CVID, by contributing to autoimmune and autoinflammatory manifestations in these patients.

## Gut Microbiota—Important Predictor of Inflammation and Autoimmunity

Over the last decade, numerous discoveries have emphasized the important role of gut microbiota (i.e., the microbial composition of the gut) in critical processes to human health including digestion, absorption of nutrients, metabolism, and immune responses. [11] Compositional and functional changes of the gut microbiome, referred to as dysbiosis, have emerged as an important contributor not only to intestinal diseases but also to systemic metabolic and inflammatory

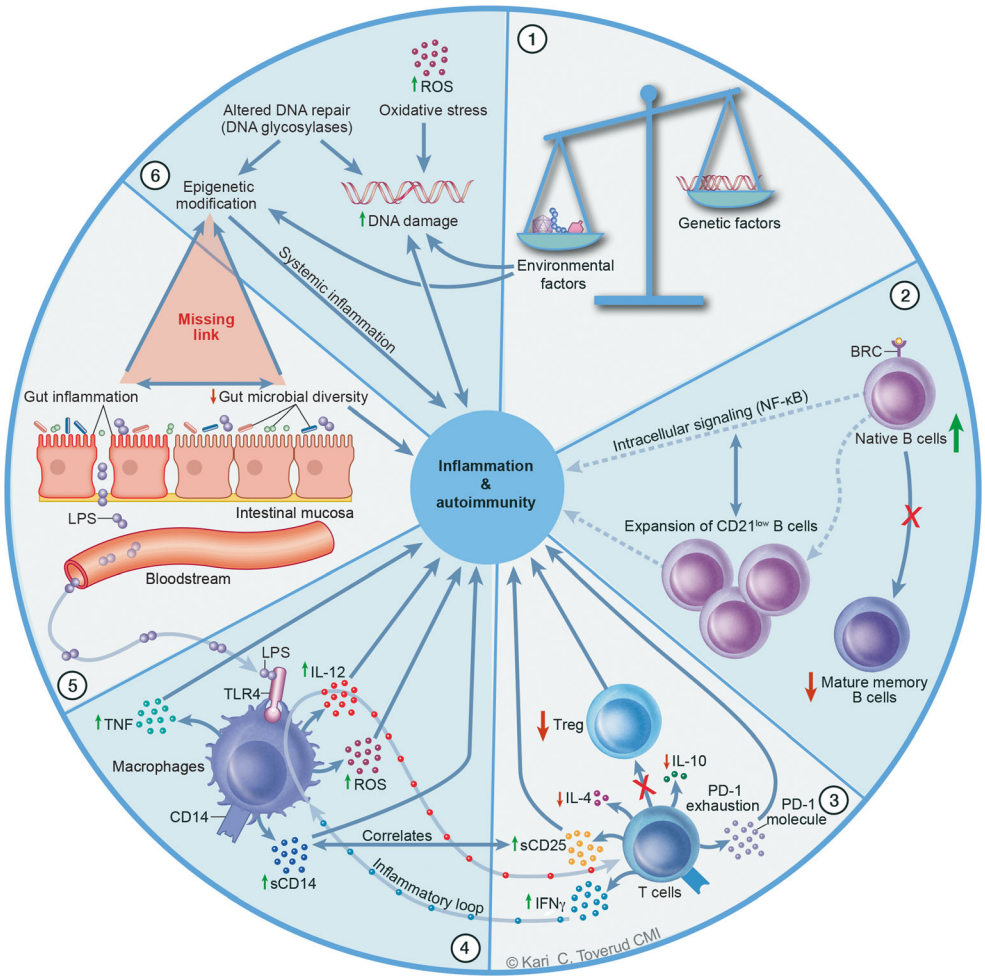


**Fig. 2 Integrated overview of suggested immunopathogenic mechanisms in common variable immunodeficiency (CVID). (1-4)** It has previously been shown that genes and environmental factors through interaction with B cells, T cells, and monocytes/ macrophages could contribute to autoimmune and inflammatory complications in CVID. We hypothesize that these known mechanisms could interact with gut microbiota and epigenetic modifications determining the autoimmune and inflammatory phenotype in CVID. **(5) Gut microbiota.** The "leaky gut theory" is one possible mechanism contributing to systemic immune activation and inflammation in CVID. When tight junctions between epithelial cells in the intestinal mucosa are compromised due to gut inflammation, there is an influx of bacterial products like LPS and other foreign substances. LPS activates the immune system through TLR4 receptors on macrophages/monocytes. These cells cause systemic inflammation through the release of inflammatory cytokines like TNF, IL-1β, and IL-12, and some of these cytokines may again induce T cell activation, which in turn induces monocyte/macrophages, leading to an inflammatory loop. **(6) Epigenetic modifications**. Epigenetic mechanisms are hypothesized to contribute to the development of inflammation and autoimmunity in CVID. Although ROS generation is a fundamental component of cellular metabolism, persistent inflammation and oxidative stress may induce tireless DNA damage and lead to mutations. Impaired DNA repair may further contribute to this, and importantly, altered function of some enzymes involved in DNA repair, i.e., certain DNA glycosylases, may also contribute to epigenetic modifications in CVID and may be the reason why some CVID patients develop inflammation and autoimmunity, whereas others do not

conditions [12–15]. The gut microbiota is also important for the development and maturation of the immune system. Germ-free mice, completely lacking a gut microbial flora, fail to develop isolated lymphoid follicles (ILF) and they are also deficient in secretory IgA. However, if they are colonized with commensal bacteria, the intestinal IgA response and maturation of ILFs occur [16–18]. Studies of immune-deficient mice lacking B and T cells, or both, have shown that these mice have considerably less diverse gut microbiota compared with littermates, or with wild-type animals raised in the same facility [19]. Furthermore, murine models have also shown that the absence of IgA or impaired IgA selection affects the balance of the gut microbiota resulting in an immense activation of the systemic immune system [19–22]. These mice studies prove a link between immunodeficiency, gut microbiota, and systemic inflammation. Previously, gene expression profiles of intestinal biopsies from three patients with CVID have suggested microbiota-induced changes that could influence B cell development [23], and Perreau *et al.* have suggested that gut microbiota-derived endotoxins (i.e., LPS) could induce T cell pathology in CVID [24]. However, Litzman *et al.* were not able to detect increased serum levels of LPS in 35 CVID patients compared to controls [25]. Based on the above findings, we have recently explored the role of gut microbiota in 44 CVID patients [26]. We found a large shift in the gut microbial composition and reduced diversity of the gut microbiota in CVID patients compared to healthy controls, without obvious associations to antibiotics use. In addition to increased plasma levels of sCD25 and sCD14 in CVID patients, as markers of enhanced T cell and monocyte activation, respectively, we also showed increased plasma levels of LPS in CVID patients ($n = 104$) compared with healthy controls ($n = 30$). The findings of increased sCD14, sCD25, and LPS were significantly higher in the patients with inflammatory and autoimmune complications compared with patients in the infection only subgroup [26]. Although serum sCD14 is frequently considered a specific and sensitive marker of LPS bioactivity in the blood [27], no correlation between sCD14 and LPS levels were found in our study, suggesting that monocyte activation could involve mechanisms independent of LPS. The CVID patients with inflammatory and autoimmune complications had a significant lower gut microbial diversity compared to healthy controls although the infection burden was the same in the two groups. There was also a negative correlation between gut microbial diversity and T cell activation as assessed by increased levels of sCD25 and increased LPS levels. These findings suggest a link between immune activation, gut leakage, and gut microbial diversity in CVID. The large shifts in the gut microbiota profile with associated increased LPS and sCD25 levels provide new clues to disease mechanisms influencing immune activation and development of complications in CVID. Previously, in a separate study, we have shown that a large proportion of the CVID patients had chronic inflammation of the gastrointestinal tract [28]. The chronic inflammation occurs both in asymptomatic and symptomatic patients. Such inflammation can cause a breach of barrier in the mucosal layer and potentially be a source of microbial translocation, which in turn can cause the systemic immune activation seen in CVID. Similar mechanisms are already described in chronic HIV infection, where microbial translocation (measured as LPS) leads to systemic immune activation [29]. The increase in LPS, particularly in the patients with non-infectious complications, supports that such a translocation may occur also in CVID. Although symptomatic GI disease often occur later during the clinical course, the fact that GI inflammation often is the asymptomatic support that the subclinical disturbance of the GI barrier can occur early on in the disease process. In addition, the altered gut microbiota in CVID is also likely to promote more subtle changes in immunological and metabolic pathways in the intestinal wall, irrespective of LPS and strict gut-leakage mechanisms [23]. Interestingly, very recently, Shulzhenko reported that CVID patients with duodenal inflammation and malabsorption were characterized by low mucosal IgA levels [30] . These patients also had increased occurrence of certain bacteria in the duodenal microbial community (i.e., *Acinetobacter baumannii)*, and they also showed that these bacteria could induce an inflammatory phenotype in macrophages. These findings further support a role for the gut microbiota in promoting immune activation and inflammation in CVID. Finally, follicular helper T ($T_{FH}$) cells have an important role in B cell terminal differentiation to memory B cells and plasma cells, and disturbed number and function has been implicated in both hypogammaglobulinemia and autoimmunity [31, 32]. More recently, the altered function of these cells have been implicated in the pathogenesis of CVID, in particular in relation to autoimmune and inflammatory manifestations. Notably, a recent study by Teng *et al.* showed that gut microbiota could promote systemic inflammation by driving the induction and egress of gut $T_{FH}$ cells [33].

## Epigenetic Modifications in CVID—a Potential Link to Systemic Inflammation

Epigenetic mechanisms, "turning genes on and off," may be the reason why genetically susceptible individuals with a polygenic risk profile develop CVID (Fig. 1). In an epigenetic model of disease development, genetic variability could be introduced at any age, and will not necessarily manifest itself as the sudden appearance of the disease, but rather as a gradual loss of cellular function. The incremental presentation of immunodeficiency seen in many CVID patients is compatible with such an epigenetic pathogenesis. Immune cells such as macrophages and B and T cells are important contributors to the immune dysregulation in CVID and are potentially more

susceptible to epigenetic changes due to the need of rapid morphological and functional changes in response to foreign bodies [34]. There are a few studies on the potential role of abnormal epigenetic regulation with regard to B cell function in CVID: (i) The loss-of-function of the E(var) chromatin-remodeling complex component INO80 was associated with impaired class switch recombination in B cells and a clinical phenotype resembling CVID [35, 36]; (ii) Increased hypermethylation of key genes within B cells lead to the repression of key B cell developmental transcription factors in cases of equine CVID [37]; (iii) In a case of monozygotic twins discordant for CVID, CpG hypermethylation, with failure of demethylation was found in the twin with CVID compared to the healthy twin and control subjects. This hypermethylation was seen in several genes of relevance in B cell development such as *PIK3CD*, *BCL2L1*, *RPS6KB2*, *TCF3*, and *KCNN4* [36, 38]. Several of these genes are involved in the transition from naive to unswitched and switched memory cells. Therefore, Rodríguez-Cortez et al. suggested that the altered epigenetic signature in memory cells in CVID individuals, resulting in hypermethylation of certain genes, could account for their decreased survival in CVID patients, potentially representing a new target for therapeutic intervention [38].

An increased burden of DNA damage, as seen in conditions characterized by persistent inflammation and oxidative stress as CVID [39, 40], may overwhelm the cellular capacity for repair and subsequently lead to base substitution mutations like 8-oxoG. Thus, a certain *NEIL3* mutation, a DNA glycosylase part of the base excision repair (BER) pathway for the repairmen of oxidative-induced DNA damage, was found in patients with fatal recurrent infections, severe autoimmunity, and hypogammaglobulinemia [41]. However, these patients also had loss of function in the *LRBA* gene which is an established cause of immunodeficiency and autoimmunity [42]. Thus, although *Neil3*-deficient mice had some signs of inflammation and autoimmunity when challenged by inflammatory stimuli and the individuals with *NEIL3* mutation (and no *LRBA* mutation) had some subclinical signs of autoimmunity, any role of NEIL3 in immunodeficiency and autoimmune disorders in humans is yet to be proven. Also, UNG-encoded uracil-DNA glycosylase has been related to the hyper-IgM syndrome, a condition with some similarities to CVID [43]. In CVID, failure or reduced capacity of BER may be involved in the development of both the disease itself and its complications, but so far, these pathways have scarcely been examined in these patients. Based on some recent studies, the impaired function of the BER pathway, in particular the altered function of certain DNA glycosylases like NEIL3, could also be of importance for epigenetic modifications [44, 45]. Thus, it is tempting to hypothesize that the interaction between inflammatory and oxidative stress, DNA repair mechanisms, and epigenetic modification could be potentially important mechanisms in the pathogenesis of autoimmune and inflammatory complications in CVID (Fig. 2).

## Could Epigenetics and Microbiota Influence the Monogenic CVID Phenotype?

The discovery of gene mutations in subgroups of CVID patients explaining their phenotype has been a great breakthrough in the CVID research field. Thus, the role of *CTLA-4* mutation and the related *LRBA*- mutation has enlightened the of role regulatory T cells in the development of immundysregulatory disorders [42, 46]. Mutations in the gene-encoding nuclear factor κB (NF-κB) subunit were reported to be the most common genetic defect in a large cohort of 390 patients with CVID, accounting for 16 (4%) cases [47]. This genetic defect has been related to CVID patients with an expanded $CD21^{low}CD38^{low}$ B cell subset and increased the frequency of autoimmunity [48]. Furthermore, a gain of function of *PIK3CD* has been found in some CVID patients and seems more likely to occur in patients with defective B and T cell responses than in patients with a pure B cell/hypogammaglobulinemia phenotype [49–51]. As mentioned above, Rodríguez-Cortez *et al.* showed significant changes in DNA methylation associated with CVID, specifically the hypermethylation of several genes of relevance in B cell function, including *PIK3CD*, illustrating a potential role for epigenetics even in monogenic forms of CVID [38]. There are now emerging data suggesting that monogenic disease identified in CVID show diverging phenotypes [46, 52]. It is tempting to hypothesize that epigenetic modification, e.g., altered methylation and/or hydroxymethylation, could play a role also in monogenic disease with incomplete penetrance and diverge phenotypes as suggested in Fig. 1. In addition, unidentified gene-gene interactions and environmental triggers as well as gut microbial composition, could hypothetically also be involved in both penetrances of disease or phenotype either directly or through epigenetic mechanisms. Thus, even in monogenic CVID disease, the patient's phenotype may be influenced by factors such as gut microbiota and epigenetic modification, and increased knowledge of these mechanisms could also be valuable in the management of monogenic CVID patients.

## CVID: a Crosstalk Between Immunodeficiency, Autoimmunity, and Inflammation with Gut Microbiota and Epigenetic Modifications as Two Potential Interacting Missing Links

Recently, the interaction between gut microbiota and local (intestinal) and systemic inflammation has received much attention as a possible pathogenic mechanism in several autoimmune and systemic immune-mediated disorders [53–55]. Based on our recent publications [26, 28], we suggest that the gut microbiota and the GI tract mucosa are involved in

mechanisms leading to autoimmunity and inflammation in CVID. These proposed mechanisms add to the already described immunopathogenic characteristics of CVID (Fig. 2). In order to target the gut microbiota for therapy in CVID, there is a need for studies exploring how altered gut environment influences systemic inflammation and other characteristics of the disease process in CVID. Whether and how the gut microbiota contributes to autoimmune and inflammatory pathogeneses in CVID remains uncertain. Future studies should concentrate on the potential to therapeutically manipulate the gut microbiota, e.g., using drugs, diet, probiotics, fecal transplant, or perhaps more relevant targeted therapy against certain microbes that are of particular importance for mediating systemic inflammation and autoimmunity.

The proposed complex picture of CVID immunopathogenesis involves an interplay of genes, environmental factors, and dysregulation of immune cells, where gut microbiota and GI inflammation can both be important contributors or endpoints to the systemic immune activation seen in CVID, and where epigenetic mechanism may be the undiscovered link between these contributors. These hypotheses, however, need to be proven by further studies. In our opinion, these pathways could represent novel targets for therapy in CVID directed against autoimmune and inflammatory manifestations that represent the most severe complications in these patients. Considering the heterogeneous nature of CVID these mechanisms may not be present in all patients, and different complications may be triggered by different risk factors. CVID is really a variable disease and in the future, there is clearly a need for a more personalized medicine based on both genotypic and phenotypic findings.

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## Compliance with Ethical Standards

**Conflict of Interest** The authors declare that they have no competing interests.

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