Common Variable Immunodeficiency: Epidemiology, Pathogenesis, Clinical manifestations, Diagnosis, Classification and Management

Running title: Common Variable Immunodeficiency

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Abstract

Common variable immunodeficiency (CVID) is a heterogeneous disorder characterized by hypogammaglobulinemia and increased susceptibility to recurrent bacterial infections. It is the most frequent symptomatic antibody deficiency with a wide variety of infectious and non-infectious complications. Numerous studies demonstrated that different immunological and genetic defects are involved in the pathogenesis of CVID. However, in most cases, the genetic background of the disease remains unidentified. This review aims to discuss different aspects of CVID including epidemiology, pathogenesis, symptoms, diagnosis, classifications and management of the disease.

Key words: Common variable immunodeficiency; epidemiology; pathogenesis; symptoms; diagnosis; classifications; management.

Resumen

La inmunodeficiencia variable común (CVID) es un trastorno heterogéneo caracterizado por una hipogammaglobulinemia y por una mayor susceptibilidad a infecciones bacterianas recurrentes. Se trata de la inmunodeficiencia humoral sintomática más frecuente y cursa con una extensa variedad de complicaciones infecciosas y no infecciosas. En la patogenia de la CVID están involucrados diferentes defectos inmunológicos y genéticos. Sin embargo, en la mayoría de los casos, el fondo genético de la enfermedad permanece sin identificar. Esta revisión tiene como objetivo discutir diferentes aspectos de la CVID, incluyendo epidemiología, patogenia, síntomas, diagnóstico, clasificaciones y tratamiento de la enfermedad.

Palabras clave: inmunodeficiencia variable común; epidemiología; patogenia; síntomas; diagnóstico; clasificaciones; tratamiento.

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1. Introduction

Common variable immunodeficiency (CVID) is the most common symptomatic primary immunodeficiency (PID) characterized by hypogammaglobulinemia and impaired specific immunoglobulin (Ig) production. Patients with CVID present a broad range of clinical manifestations including recurrent bacterial infections, autoimmunity, interstitial lung disease, enteropathy, lymphoproliferation, malignancy and allergic diseases [1, 2]. In recent years, several monogenic defects involved in the presentation of CVID have been identified; however, these genetic defects account for less than 20% of CVID patients in non-consanguineous cohorts [3] and approximately 70% of CVID patients in consanguineous cohorts [4]. Furthermore, several abnormalities in the innate and adaptive immunities have been reported [5-7], however, the exact molecular defects leading to CVID is still unknown.

Based on various clinical manifestations and immunological data, some classifications have been defined for CVID patients [8]. Since CVID is considered as a heterogeneous group of PIDs with various clinical and immunological features, an appropriate classification for these patients is essential. Regarding diagnosis of CVID, knowing clinical features along with immunological and genetic analysis are most important. Clinical heterogeneity in CVID patients has led to diagnostic challenges and difficulties in determining the optimal treatments for patients [9]. Although immunoglobulin therapy is the mainstay of the treatment for CVID patients, hematopoietic stem cell transplantation (HSCT) is utilized for CVID patients mostly associated with cellular immune defects and therapy resistant autoimmunity. HSCT a potentially curative treatment approach has been performed in some cases of CVID with mixed results. Few studies also showed the advantage of new immunomodulation via targeted treatment in a selected group of CVID patients with specific genetic defects [10].

The aim of this review is to present a comprehensive view of common variable immunodeficiency including Epidemiology, Pathogenesis, Clinical manifestations, Diagnosis and also Classification of the disease.

2. Epidemiology

Antibody deficiencies are the most common defect among primary immunodeficiencies and account for 30-70% of all patients identified with a specific defect. Within the PID group, CVID is the most frequent symptomatic antibody deficiency [11]. According to a recent report by the Jeffrey Modell

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centers network, there are important geographic disparities in terms of CVID prevalence for North America (n=6443), Europe (n=4279), Asia (n=459), Australia (n=657) and Africa (n=156) [12]. The highest prevalence of CVID has been documented in the USA (40.2% of all PID patients) whilst the lowest rates were observed in Middle East countries 2.6% and Africa with only 1.3% [12]. The most likely reasons responsible for these differences are the availability of appropriate diagnostic methods, registry and PID awareness [13].

In CVID the age of onset is associated with the predominant clinical manifestations. The United States Immunodeficiency Network (USIDNET) database compared patients diagnosed in the pediatric age (17 years and younger) to patients with adult onset (18 years or older) CVID. Based on this epidemiological study (n=457 patients), otitis media, developmental delay and failure to thrive were more frequent in pediatric-onset CVID patients, whilst bronchitis, arthritis, and fatigue were more common in adult CVID patients [14].

3. Pathogenesis

In previous years, various studies have investigated the pathogenesis of CVID. The identification of monogenetic CVID causes has increased our understanding of this complex disease [9, 15]. In addition, recent studies demonstrated a role of epigenetic modifications in the development of CVID disorder [16, 17]. Gene mutations at three levels of the surface, cytoplasmic, and nuclear of cells have provided in **Tables 1, 2 and 3**, respectively.

3.1. Gene and Molecule defects

Different members of the Tumor necrosis factor (TNF) receptor superfamily have been reported to be involved in the pathogenesis of CVID. In this pathway, single gene defects in trans membrane activator and calcium modulator and cyclophilin ligand interactor (TACI, encoded by *TNFRSF13B*), B cell activating factor belonging to the tumor necrosis factor family BAFF receptor (BAFF-R, encoded by *TNFRSF13C*), TNF-like weak inducer of apoptosis (TWEAK, encoded by *TNFRSF12*) and CD27 encoded by *TNFRSF7* have been described. BAFF-R and TACI, are known to participate in B cell development and activation by engaging a proliferation-inducing ligand (APRIL) and/or BAFF [18, 19]. Although studies have demonstrated that 8% to 10% of CVID patients have a defect in TACI, these mutations have been also described in the general population without hypogammaglobulinemia raising the question of their pathologic impact. Since TACI regulates the function of the B-cell receptor (BCR), Toll-like receptor (TLR) 7 and 9 molecules, defects in molecules could result in impairment of B cell activation/maturation, which then may contribute to the development of

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autoimmune manifestation [18, 20]. In addition to the TNF receptor superfamily, defects in the CD19 complex (CD19, CD21, and CD81) or co-stimulatory molecules such as CD20 and IL-21 receptor have also been described in CVID patients. These molecules are important for the adequate development, maturation and survival of B cells and are likely involved in the CVID pathogenesis [5]. Furthermore, defects in two co-stimulatory and inhibitory receptors located on T cells (inducible costimulator, ICOS and cytotoxic T-Lymphocyte Associated Protein 4, CTLA-4) were identified in a group of CVID-like patients with associated T cell abnormalities [5].

The last years have revealed defects in several signaling-associated molecules at three levels of the surface, cytoplasmic, and nuclear molecules implicated in the pathogenesis of CVID patients. The detailed functions and effects of the most important defects are summarized in **Tables 1, 2 and 3**. Nowadays, each defective molecule is considered as a separate form of immunodeficiency and is categorized as monogenic disorders. In this sense, IUIS (International Union of Immunological Societies) classification classified PID disorders in the specific categories [21].

3.2. Epigenetic changes

In recent years several studies have highlighted the role of epigenetic factors in the pathogenesis of CVID [16, 17, 22, 23]. Epigenetic mechanisms can influence gene expression without altering the germ-line DNA gene sequences and play an important role in the normal developmental program of immune cells [16]. The mechanisms described so far, include DNA methylation, chromatin modulation, histone modification, transcription factor expression and non-coding RNAs (ncRNAs) [24].

DNA methylation is catalyzed by DNA methyltransferases (DNMTs) and represses gene expression by reducing transcription factors and DNA regulatory elements or by making DNA fragments inaccessible to transcription factors [25]. This mechanism plays an important role in both, early and late stages, of B cells development. The study of twins discordant for the CVID diagnosis revealed a higher degree of DNA methylation in the switched and non-switched memory B cells of the patient when compared to the healthy sibling. Furthermore, hypermethylation of genes such as *PIK3CD, BCL2L1, RPS6KB2, TCF3*, and *KCNN4* in B cells was observed and demethylation during the transition from naive to memory cells was impaired. This observation revealed a novel mechanism responsible for the defective generation of memory cells in CVID patients [17]. Using an equine CVID model, methylation disturbance in the form of hypermethylation of PAX5 was shown to block B cell development, to reduce B cell numbers and finally to the development of late-onset CVID [22].

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Other factors implicated in the epigenetic regulation of B cells are non-coding RNAs (ncRNAs) [26]. ncRNAs exert their regulatory functions by mRNA post-transcriptional changes or influencing DNA transcription [26]. miRNAs, a subgroup of short ncRNAs that mainly represses gene expression, contribute to the regulation of different stages of B cells development. Studies on the role of miRNAs in the pathogenesis of human CVID are still ongoing; however, mouse models have already demonstrated the importance of these molecules for T and B cell development [27]. Importantly, knockout mice lacking miR-142 [23] or miRNA-155 [27] exhibit immunological features similar to those observed in CVID patients.

Histone and chromatin modifications are an epigenetic mechanism that might be also involved in the CVID pathogenesis. Defects in histone and chromatin modification enzymes have been described in patients with Kabuki syndrome, a complex multi-system syndrome that includes hypogammaglobulinemia, reduced naïve and switched memory B cells and an increase of a $CD21^{low}$ B cell population features often found in patients with CVID. In the Kabuki setting, the B cell differentiation defect was shown to be associated with an impaired histone modification process which is fundamental for the correct B cell development [28].

3.3. Microbiome dysbiosis. The human microbiome interacts with the systemic immune system via immune cells and some bacteria that may cross the gut epithelium, exposing the systemic immune system to microbial components [29]. Bacterial products such as lipopolysaccharide (LPS) can activate the immune response through recognition of microbe-associated molecular patterns by the innate immune system [30]. Microbial dysbiosis may lead to the overgrowth of proinflammatory bacteria or a decrease of anti-inflammatory bacteria which subsequently leads to a further imbalance of the immune system [31].

Importantly CVID patients have extensive microbial dysbiosis with a reduced alpha diversity and differences in the taxonomic profile when compared to patients with inflammatory bowel disease (IBD). This reduction of alpha diversity in CVID patients is associated with raised T-cell activation markers including LPS and sCD25 and decreased levels of plasma IgA, suggesting that the altered gut microbiota profile could modulate the gut permeability with subsequent LPS and sCD25 elevation and decreased IgA level along with chronic immune activation in CVID [32]. Nevertheless, attributing causality to microbial changes due to the presence of low IgA level and impaired epithelial gut barrier remains challenging and further research in this field is clearly needed.

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4. Immune cell abnormalities

Defects in the adaptive and innate immune system and in particular abnormal B cell and T cell numbers have been reported in CVID patients. Although the classic immunological defect in CVID is related to plasma cell abnormalities, alterations of other B cells subsets are not uncommon. **Table 4** gives an overview of the so far described immune cell abnormalities in CVID.

4.1. B cell subsets

B cell development involves sequential steps of maturation initiated in the bone marrow and completed in peripheral compartments. Immature B cells pass through transitional stages and become either marginal zone B cells or follicular naïve B cells in the periphery. In germinal centers, follicular B cells differentiate to switched memory B cells and antibody secreting plasma cells, whereas marginal zone B cells evolve to IgM memory B cell [33, 34]. The majority of studies demonstrated that almost 90% of CVID patients have normal B cell counts, [35, 36], indicating that the major defect is likely related to the alterations of the terminal stages of B-cells differentiation. Furthermore, several groups including our own have shown that disturbed B-cell subsets could be the result of an increase of terminal B-cell apoptosis [37, 38]. The impaired antibody production despite normal B cell counts also suggests a defect in the differentiation of B cells into memory and plasma cells in many CVID patients [35].

Several studies have reported decreased IgM memory B cells ($CD19^+/CD27^+$), class switched memory B cells ($CD19^+/CD27^+/IgD^-/IgM^-$) and plasma cells in CVID patients [34, 39, 40]. Since the correct germinal center formation is essential for the development of switched memory B cells in secondary lymphoid organs, it seems that the reduction of switched memory B cells is highly related to the impaired germinal center reaction. In contrast, a profound expansion of the transitional B cell pool has been observed in two siblings with CVID disorder (especially BAFF-R deficiency) due to a block in the transition from T1 to T2 cells [41-43]. Furthermore, it has been reported that a subgroup of CVID patients manifests with the expansion of a special subset of B cells called $CD21^{low}$ B cells. This subset is distinct from other B cell subsets as it shows low expressions of CD21 and CD38 simultaneously [43]. In one study, it has been demonstrated that its expansion is associated with an abundance of IFN-γ producing $CD4^+$ $CXCR5^+$ follicular T helpers (TFH) cells and immune dysregulation in CVID patients [44].

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The characterization of signaling pathways essential for B-cell differentiation and class-switch recombination (CSR) have been evaluated by Taraldsrud et al. [45]. In this study constitutive phosphorylation levels of signal transducer and activator of transcription (STAT 3,-5 and -6), phosphoinositide phospholipase C-γ, Erk, and Syk were significantly increased in B cells of selected CVID patients with non-infectious complications. In the future, the combination of surface marker determination together with kinase phosphorylation pattern may allow developing a model able to predict the occurrence of non-infectious complications in CVID patients.

4.2. T cell subsets

T cell abnormalities have been reported in CVID patients. These abnormalities are broad and include total numbers, percentages, surface markers and function of different T cell subpopulations [5]. Some studies showed a reduction of the total, naïve and memory $CD4^+$ T cells, recent thymic emigrants (RTE) and an increase in activated $CD4^+$ T cells [46]. Decreased thymic output, enhanced T cell turnover and spontaneous apoptosis lead to $CD4^+$ T cell count reduction [46], whereas the observed increase of activation of $CD4^+$ T cells might be due to low regulatory B cell (Breg) numbers and defective Breg responses after T-cell stimulation [47]. It has been demonstrated that CVID patients with a profound reduction in $CD4^+$ T cell counts are more likely to develop autoimmunity and lymphoproliferation, indicating that there is a strong correlation between the frequency of naïve $CD4^+$ T cells and clinical manifestations. Despite T cell abnormalities reported in CVID patients, however, based on discrepancies of different criteria for diagnosis, it is not clear whether patients with such defects should be considered affected with CVID or with late onset combined immunodeficiency (LOCID) or other forms of combined immunodeficiencies [48, 49].

There is still a controversy regarding the role of the different T helper subsets for the pathophysiology or development of clinical manifestations in CVID patients, it has been reported that type 2 helper (TH2) cytokine levels such as IL-4 and IL-10 are significantly elevated in CVID patients, whilst this increase was not observed for TH1 cytokines [50]. Similarly, it has been reported that the serum level of CD30 (an indicator of TH2 cytokine production) is increased in CVID patients [50], suggesting that CVID patients might be skewed towards TH2 responses. However, other studies report excessive TH1 responses in CVID patients [51, 52]. This discrepancy is likely due to heterogeneous CVID etiologies, differences in the composition of patient cohorts and experimental methodology.

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TH17 cells have also been investigated in CVID patients. TH17 cells and its related cytokines IL-17A, IL-17F, IL-22 and IL-21 are involved in the host defense against extracellular bacterial and fungal infections and also play an important role in inflammatory diseases. Barbosa et al. reported a decrease in the frequency of circulating TH17 cells in CVID patients [53]. Moreover, another study demonstrated a reduction of TH17 cell–specific gene expression in CVID patients when compared to the healthy controls [54]. A negative correlation between TH17 cells, probably due to its regulatory role on the appropriate function of the germinal center, and the expansion of activated $CD21^{low}$ B cells has been observed [36, 43, 44]. Regarding TFH in CVID patients, some studies have identified increased TFH counts [55, 56], whereas a decrease in TFH cells has been observed in both ICOS-deficient mice and patients [57, 58]. Since TFH cells express ICOS in its surface, decreased TFH counts are the logical consequence in patients with ICOS deficiency.

Regulatory T cells (Tregs) are important regulators of the immune system and play a crucial role in the maintenance of self-tolerance [59]. Although Kutukculer et al. did not observe significant differences between the percentages and absolute counts of Treg in CVID patients when compared to healthy controls and therefore concluded that Treg cells are not relevant for the pathogenesis of CVID [60] whereas the results of other studies suggest that a reduction in the Treg counts can influence disease manifestations and identified a correlation between Treg counts and autoimmune manifestation, granulomatous lesion and splenomegaly [61, 62]. Furthermore, it has been showed that sorted Treg cells from patients with CVID are less effective in suppressing proliferation of autologous and allogenic effector $CD4^+$ T cells than CVID patients without autoimmunity [63] and that the decrease of Treg cells correlates with the expansion of $CD21^{low}$ B cells in CVID patients with autoimmunity [64].

Similar to $CD4^+$ T cells, a decline in the frequency of $CD8^+$ T cells subsets has been demonstrated. Naïve and effector memory $CD8^+$ T cells numbers are reduced whereas higher percentages of activated $CD8^+$ T cells have been reported [48, 65, 66]. Studies showed that $CD8^+HLA\text{-}DR^+$, $CD8^+CD38^+$, and $CD8^+CD38^+HLA\text{-}DR^+$ T-cell counts are higher in CVID patients and also that this increase is restricted to patients with clinical complications including autoimmune disease, splenomegaly, lymphoid proliferation, and granulomatous disease [65]. Moreover, higher expression levels of Granzyme B in $CD8^+$ T cells correlate with autoimmune manifestations in CVID patients [67]. Viallard et al showed that patients with low $CD27^+$ B cells had higher percentages of HLA-DR CD8 T^+ cells with a differentiated effector phenotype [68]. These data further confirm a higher activation status of $CD8^+$ cells in CVID patient [69]. Finally, Paquin-Proulx et al. found a specific subset of γδ T

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cells expanded in CVID patients. Although they suggested that this deviation in γδ T cell subsets is a general feature of CVID patients further studies are needed to confirm this observation [70].

4.3. Dendritic Cells (DC)

Dendritic cells play an important role in the induction of T cells responses as well as in the differentiation of naïve B cells to plasma cells. Studies about dendritic cells in CVID patients have shown a progressive decline of these cells as well as maturation and function abnormalities [71]. In this regard, the expression of maturation and costimulatory molecules such as CD80, CD86 and HLA-DR and also the production of IL-12 were lower in CVID patients [71, 72]. Furthermore, decreased IFN-α production upon TLR-9 stimulation in plasmacytoid dendritic cells has been demonstrated [63, 73]. In contrast, Taraldsrud et al. reported that DCs of CVID patients have a normal response to TLR-7 and TLR-9 and viral stimulation as well as have normal numbers of DC progenitor cells in the bone marrow [74]. Overall, based on the prominent role in presenting antigens to T cells and initiation of primary immune responses, abnormalities in DCs may lead to a defect in the generation of antigen specific $CD4^+$ T cells and also impaired antibody production as those seen in CVID patients.

4.4. Monocytes/Macrophages

Monocytes from CVID patients exhibit significantly increased reactive oxygen species (ROS) generation which might result in specific clinical manifestation including malignancies, autoimmune disorders, and some acute and chronic pulmonary diseases [75]. Aukrust et al. suggested that persistently increased TNF levels and TNF receptor expression might contribute to the activation of monocytes/macrophages [76]. Moreover, it has been demonstrated that increased IL-12 production in $CD14^+$ monocytes results in skewing T cell responses toward TH1. In addition, overexpression of IL12 leads to the upregulation of IFN-γ in T cell subsets and subsequently skews the immune system away from the TH2 responses to TH1 [77]. Thus, it seems that the altered cytokine profile in monocytes is a probable mechanism contributing to the enhanced TH1 profile and by this to defective antibody production in a selected group of CVID patients.

In the absence of additional cytokines, the tendency of monocytes (mainly CD83 negative) from CVID patients to form giant cells is almost twice as high when compared to normal cells. However, the excess of cytokines such as IL4, GMCSF, IFNγ, TNFa contribute to 5 fold increased monocyte fusion index in CVID. A higher fusion index contributes to granuloma formation (a lymphoproliferative complication) and is related to chronic inflammation (e.g. inflammatory cytokines, particularly IFNγ and TNF) and lymphocyte concentration. Of note, *in vitro* the fusion rate of monocytes treated with Ig

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products can be increased which raises the debate of whether this standard treatment is involved in the risk of granulomatous disease, possibly by enhancing FcγRI expression [78].

4.5. Innate lymphoid cells (ILC)

Innate lymphoid cells (ILC) are a group of immune effector cells characterized by lymphoid morphology but lacking the B and T cell receptor. They play an important role in innate immunity, tissue development and cytokine production [79]. Based on phenotypic and functional characteristics, ILCs are classified into three major groups. Group 1 comprise NK cells and other noncytotoxic ILCs, defined by T-bet expression and IFN-γ production; group 2 express GATA-3 and produce type 2 cytokines such as IL-4, IL-5 and IL-13; group 3 contain the transcription factor RORγT and are capable to produce IL-17 and IL-22 [79]. A recent study demonstrated that the numbers of IL-17^{+}CD127^{+}Thy-1^{+} Lin^{-} ILCs are decreased in CVID patients [54]. Conversely, another study indicated a significantly expanded population of Lin^{-}CD127^{+} cells producing IFN-γ, IL-17A and IL-22 and it has been suggested that the expansion of these cells is characteristic for CVID patient with inflammatory manifestations [80].

Regarding the ILC1 group, the frequency and function of NK cells have been also evaluated in CVID patients. NK cells are a component of the innate immune system and play an important role in the killing of the tumor and virally infected cells [81, 82]. Kutukculer et al. reported increased numbers of $CD3^{-}$CD16^{+}CD56^{+}CD28^{+} NK cells whilst $CD28^{-}$ NK cells were significantly decreased in CVID patients. This augmentation could be related to the presence of a compensatory mechanism for protection against tumor development and viral infections [83], as high frequency of bacterial infections and non-infectious disease especially viral infections and tumor development have been observed in CVID patients with NK deficiency [82].

$CD117^{+}$ILCs group 2 have a role in the generation of antibody production. It has been recently reported that the number of these cells are reduced in patients with CVID (with impaired response to IL-2, -7, -25 and -33) [84]. These patients manifest with an increased prevalence of chronic enteropathy and an immunologic profile of lower numbers of peripheral marginal zone-like B cells [84].

4.6 NKT

NKT cells are a group of lymphocytes with a rearranged Va14-Ja18 TCR that recognizes glycolipids and are able to produce TH1 and TH2 cytokines upon stimulation. In a study by Carvalho et al, it has

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been demonstrated that there is a dysbalance of NKT cell subsets in CVID patients as the frequency of $CD4^+$ NKT cells is higher than $CD8^+$ NKT cells [85]. However, they found that there was no difference regarding the frequency of circulating NKT cells between the patients and healthy control. In contrast, a study on iNKT cells identified a marked decrease in the proportion of these cells and was associated with low or absent switched memory B cells, supporting a potential correlation between iNKT cell and B cell function [86].

5. Clinical manifestations

5.1. Infections

Infections are the most typical clinical manifestations in CVID patients and involve the respiratory and gastrointestinal system [87]. The upper and lower respiratory tract are the most common side of infections and contribute significantly to morbidity and mortality of CVID patients [88]. Bacterial infections due to *Streptococcus spp., Haemophilus spp., Moraxella catharralis, Neisseria meningitides*, and *Staphylococcus spp.* are the major group of pathogens affecting CVID patients [88, 89]. Moreover, viral pathogens such as *Rhinovirus* and *Herpes zoster* and *Mycoplasma spp.* are more prevalent and even more persistent in CVID [90]. Although opportunistic infections including *Pneumocystis jirovecii* and *Cytomegalovirus* are not characteristic for CVID and should challenge this diagnosis, they can be found in a subgroup of patients with CVID diagnosis and low $CD4^+$ T-cells [91].

Bronchiectasis and interstitial lung disease are two important lung complications that manifest after recurrent and severe lung infections [92, 93]. Also, recurrent sinusitis, bronchitis and otitis media are found in half of the patients. Ig replacement has an important role in decreasing the infections but yet susceptibility to infections remains problematic [89]. Ig replacement treatment modifies the natural course of the disease, but mainly in terms of invasive infections, while the incidence of respiratory infections, including pneumonia may depend on several factors, such as late diagnosis with the development of bronchiectasis and immune dysregulation [88].

Gastrointestinal tract infections manifest in form of chronic or acute diarrhea [94]. Typical histopathologic findings are in the intestinal tissue of CVID patients are deep follicular lymphoid hyperplasia and reduced plasma cell numbers. *Giardia lamblia* followed by *Campylobacter jejuni* and *Salmonella spp* are the most common identified pathogens. These infections are characteristic for

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patients with undetectable serum IgA levels and intravenous Ig replacement therapy has failed to show consistent improvement of gastrointestinal symptoms [95, 96].

Despite the known increased infection susceptibility, there is no significant difference between the prevalence of *Helicobacter pylori* infection in CVID when compared to healthy individuals. One potential explanation is the relatively common prescription of prophylactic and therapeutic antibiotics in this patient group that may collaterally prevent *H pylori* infections [95, 97, 98]. However, *H pylori* infection in CVID patients should be considered and screening for CVID patients due to its role in development gastric dysplasia or gastric cancer [96, 99].

Regarding mild infections in CVID patients, a group of patients only experience infections in their life and no non-infectious complications. According to clinical phenotype classification by Chapel et al, these patients are categorized as infection only phenotype. A milder clinical severity and longer survival in these CVID patients could be due to the presence of a compensatory mechanism in memory B cell generation and IgG production after co-culture of PBMC with anti-$CD40^{+}$IL-21 and IL-4 [100, 101].

5.2. Autoimmunity

Autoimmune manifestations are common (10-30%) among PID patients [102]. Autoimmunity almost is present in 21% to 42% of these patients [103, 104]. Physicians should consider a diagnosis of CVID in patients with autoimmune features in order to prevent diagnostic and therapeutic delays [105]. Autoimmune cytopenias (Idiopathic thrombocytopenic purpura (ITP), autoimmune hemolytic anemia (AIHA) and autoimmune neutropenia) are the most common and potentially severe manifestations [106, 107], while other autoimmune manifestations like rheumatologic autoimmune disorders are also observed in these patients [108-112].

Autoimmunity is the aberrant response of the immune system to self-antigens that occurs when self-tolerance is impaired. Several factors, which influence T-cell tolerance induction such as lower T cell and Treg numbers and aberrations in cytokine secretion, have been described as mechanisms leading to autoimmunity in CVID patients [67, 113]. Class switch recombination (CSR) and somatic hyper mutation (SHM) defects, increased levels of B cell-activating factor (BAFF), impaired Toll-like receptor (TLRs) and abnormalities in lymphoid cells subsets have been reported in CVID patients and are likely associated to the development of autoimmune manifestations [111, 114-116]. It is notable that despite the low serum level of immunoglobulins and poor specific antibody response in CVID

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patients, autoantibodies are often found in a particular group of CVID cases [117]. Although intriguing, these sometimes counter intuitive observations underscore the necessity of further researches to reveal the underlying mechanisms leading to autoimmunity in CVID.

5.3. Lymphoproliferation and malignancy

An increased risk of malignancies has been reported in CVID patients [118]; however, the precise incidence and mechanism of this association are still unclear. It has been estimated that the incidence of malignancy among CVID patients is almost 2.5 % when the age at onset of symptoms is <16 years, whereas this rate is almost 8.5 % among for patients diagnosed at an older age [118]. CVID patients with polyclonal lymphadenopathy have an increased risk of lymphoid malignancies, being the overall risk for lymphoid malignancies (mostly extra-nodal non-Hodgkin's B cell lymphoma) 2-10% for CVID patients [9, 107].

Additionally CVID patients are prone to develop malignant gastric cancers [103, 119]. Impaired immunity to carcinogenic pathogens such as Epstein-Barr virus and *H pylori* potentially contributes to this. Ten-Fold gastric cancer risk has been reported in CVID [120], but this ratio has been decreased recently [9] potentially due to increased use of antibiotics at least partially treating and controlling H *pylori.* This reduces the rates of chronic atrophic gastritis and metaplasia in the gastric body, which are the most important predisposing factors for gastric adenocacinoma in CVID patients [121, 122].

5.4. Enteropathy

A selected group of CVID patients suffers from complex gastrointestinal disorders refractory to conventional treatments resulting in significant weight loss and malnutrition that in some cases require long-term parenteral feeding [107, 123]. Histopathology in tissue samples obtained from patients with small bowel disease commonly shows villous atrophy and inflammatory lymphocytic infiltrates [95, 123]. Besides the obvious nutritional, gastrointestinal and infectious complications which are shared with many other PID patients, CVID patients with this specific enteropathy phenotype are prone to develop complications due to changes of bone mineral density, granulomatous disease, lymphopenia and exhibit an overall higher mortality rate [124, 125].

5.5. Asthma and allergic diseases

Patients with CVID and IgA deficiency are predisposed to develop atopic conditions probably due to mucosal immune defects as well as immune dysregulation with skewing to towards a TH2 phenotype [126]. However, the data regarding the prevalence of atopic diseases in CVID is incomplete and only a

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few reports are available on the incidence of asthma and allergic disorders in CVID patients [126, 127]. According to the currently available data, the prevalence of allergic disorders (including asthma, allergic rhinitis, atopic dermatitis, allergic eczema, food allergy, urticaria, allergic conjunctivitis and drug allergy) ranges from 12-42% in the different CVID cohorts [126, 128]. This discrepancy could be explained by factors such as sample sizes, underlying genetic defects, and ethnic composition. It seems that immune dysregulation, major histocompatibility complex haplotypes, impaired IgA response to luminal allergen challenge, high IgE level (because of a compensatory mechanism for decreasing other antibody isotypes) and persistent pulmonary infections are major causes of asthma and other atopic diseases in CVID patients [126]. Similar to other complications, a high suspicion and prompt diagnosis of atopic disorders are important when caring for CVID patients as this likely will impact their management and quality of life.

5.6. Other clinical findings

Neurologic and liver diseases are less commonly reported in CVID patients [129]. Infectious etiologies of the nervous system have described in 43 cases and represent the biggest class of neurologic dysfunction [130, 131], followed by autoimmune/inflammatory myelitis [132, 133]. Neuroendocrine alterations [134, 135] and nutritional deficiencies (vitamin E and B12 deficiency) have been reported but are in general uncommon [136, 137]. Almost 10% of CVID patients manifest significant liver with an increase in alkaline phosphatase level [138]. Primary biliary cholangitis, granulomatous liver disease [139] and idiopathic non-cirrhotic portal hypertension (including nodular regenerative hyperplasia) are the most commonly observed manifestations in CVID patients [138, 140].

6. Diagnosis

CVID patients have a broad phenotype with heterogeneous clinical and immunological features. This contributes to diagnostic difficulties and delays. Maintaining a high index of suspicion for CVID in patients with complex clinical manifestations and following the established diagnostic criteria is warranted in order to establish a timely and precise diagnosis.

Generally, hypogammaglobulinemia and recurrent infections are the hallmarks of a CVID diagnosis [141]. Diagnostic criteria have been proposed by the ESID (European society of immune deficiencies) in 1999 and redefined in the later years using both laboratory findings and clinical symptoms [142]. The newest ESID criteria for CVID diagnosis are illustrated below:

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At least one of the following:

- increased susceptibility to infection
- autoimmune manifestations
- granulomatous disease
- unexplained polyclonal lymphoproliferation
- affected family member with antibody deficiency
- AND marked decrease of IgG and marked decrease of IgA with or without low IgM
- AND at least one of the following:
- poor antibody response to vaccines (and/or absent isohaemagglutinins);
- low switched memory B cells (<70% of age-related normal value)
- AND secondary causes of hypogammaglobulinaemia have been excluded
- AND diagnosis is established after the 4th year of life (but symptoms may be present before)
- AND no evidence of profound T-cell deficiency, defined as 2 out of the following (y=year of life):
- CD4 numbers/microliter: 2-6y <300, 6-12y <250, >12y <200
- % naive CD4: 2-6y <25%, 6-16y <20%, >16y <10%
- T cell proliferation absent

Practically, to differentiate a patient with CVID from children with other risk factors predisposing them to recurrent infections taking a family history and physical examination are helpful. Based on history and physical examination laboratory investigation should be performed, but must be supplemented by immune function testing [143]. Every screening evaluation for CVID must include a physical examination of the patient. However, clinical symptoms can vary from patient to patient, even among affected family members with identical mutations of the same gene [144-146]. After physical examination and history-taking, the physician should be suspected of PID and a set of primary para-clinical evaluation should be taken for the patient (**Figure1**).

Laboratory and para-clinical evaluations

Initial evaluation: The most useful first-line immunological investigations that target CVID and majority of common CVID-like entities includes testing for a complete blood count with differential (CBC-Diff), lymphocyte subset analysis, and measurement of serum immunoglobulin, these tests can identify children who need further testing and referral to a subspecialist [147]. Patients with CVID have low serum Ig levels and/or decreased response to vaccination [148]. Serum Ig levels vary with age, so age-specific cutoffs should be used when performing Ig assay. Protein loss should also consider in patients with low

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Ig in serum, therefore, in suspected individual serum albumin level should be checked because low albumin suggests protein loss through the kidney or malabsorption of the protein in the bowel. IgG antibody titers to vaccine antigens can be checked to determine specific antibody response. Both protein and polysaccharide antigens usually use for evaluation [149]. A vaccine with protein antigens can be checked at all ages; while immunization with polysaccharide antigens can be evaluated if the patient is 2 years or older. If the physician is using a conjugated pneumococcal vaccine, IgG antibody titers against specific serotype are needed to be measured [148].

Secondary evaluations: In addition to the global assessment of immune development through measurement of nonspecific features, such as serum immunoglobulin levels and leukocyte and lymphocyte subpopulations, evaluation of the specific immune response is essential. When a patient had abnormality in screening tests related to humoral immunity, following advanced tests are recommended to perform: IgG subclass analysis, flow cytometry to enumerate B-cell subsets (e.g., naive and switched memory cells), in vitro immunoglobulin production in response to mitogens or other stimuli, specific antibody response to immunization with ϕX174 [150].

Tertiary evaluations: Genetic testing plays a vital role in the diagnosis of CVID. There are several tools including molecular and cytogenetical tests that we can pick to exploit in genetic testing in CVID. Currently, chromosomal microarray (CMA) is useful for copy number variants (CNV) detection when no disease causing variants have detected after exome sequencing or when CNV prediction data indicated the presence of a relevant CNV [151]. CNV analysis has been performed in CVID to recognize the genetic basis of this heterogeneous immunological disorder [152, 153].

The ‘gold standard’ method of mutation screening is DNA sequencing using the dideoxy chain termination method that is considered the 1st generation of sequencing. This method is highly accurate and can detect point mutations, and some deletions and duplications. Sanger sequencing is applied in the diagnosis of circumstances that one gene or small set of gens is most likely causative. Sanger sequencing is a necessary tool for validation of variants detected using high throughput sequencing and also a reliable and cost effective method for evaluating family members of an affected patient for known mutations (segregation analysis) [4].

Next-generation sequencing (NGS) has a great implementation on clinical diagnostics for many genetic diseases. Currently, three NGS technologies including targeted sequencing (TGS), whole exome sequencing (WES) and whole genome sequencing (WGS) are in molecular service of diagnosis and

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research in CVID and its new entities. The most focused NGS approach is the TGS, which sequences customizable sets of genetic targets covering a known group of disease-causing genes. The utility of TGS is inherently limited because this approach is restricted to a set list of target genes. However, in the situations that we have a list of multiple possible genes, TGP is reasonable. WES is a focused technology that sequences only the protein-coding regions, which contain around 85% of disease-causing mutations and cover 90 to 95% of exomes [154]. As the most of known monogenic causes of CVID-like phenotypes were identified in individual patients, rather than large families [155], it may not be rational to use TGS in patients with complex phenotypes that the novel causative gene is possible. The most comprehensive NGS technique is WGS, which covers the entire span of human DNA, including both coding and noncoding regions. Currently, WGS is not widely used clinically in CVID and it is the final choice where previous methods like TGP or WES cannot find causative variation [156]. Finally, a genetic investigation of patients can be helpful for a better prognosis, better defining the follow up and also genetic concealing.

7. Classification

CVID patients manifest various clinical and immunological features, thus the classification of these patients seems to be imperative. To date, several classifications have been proposed based on clinical manifestations and laboratory data in CVID patients. The Freiburg classification was established in 2002 by Warnatz et al. based on switched memory and $CD21^{low}$ B cells. Later, Piqueras et al. suggested the Paris classification based on memory B cells populations only. Wehr et al. established a comprehensive classification in 2008 that is now known as EUROclass [41]. Recently, a fourth classification based on B cell subset abnormalities has been defined by Driessen et al. [8].

7.1. Freiburg classification

The Freiburg classification distinguishes CVID patients based on the percentages of switched memory and $CD21^{low}$ B cells. Indeed, this classification discriminates patients with disturbed germinal center reactions and defective early peripheral B cell differentiation by analyzing CD21 expression. In this classification, patients are categorized into 2 groups based on the expression of IgM, IgD, CD27 (as a marker for Memory B cells) and CD21. Group I with severely reduced class-switched memory $CD27^{+}IgM^{-}IgD^{-}$ B cells (switched memory B-cells < 0.4%) and group II with normal switched memory B-cells > 0.4%. Furthermore, type I patients are subdivided into group Ia with highly expanded $CD21^{low}$ B cells ($CD21^{low}$B-cells >20%) and group Ib with percentages of $CD21^{low}$B-cells <20%. Splenomegaly and/or autoimmune manifestations are characteristic features of group Ia [8, 36, 40].

7.2. Paris Classification

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The percentages of switched memory B cells and total $CD27^+$ B cells are used for this classification. Patients with a reduced percentage of $CD27^+$B cells < 11% represent the group MB0, while patients with decreased class-switched memory B-cells < 8% and increased total $CD27^+$ B cell >11% of B-cells are classified as MB1. Group MB2 refers to patients who not fulfill the MB0 or MB1 criteria. According to this classification, the incidence of splenomegaly, granulomatous disease or lymphoid proliferation was higher in patients of group MB0 when compared to MB1, whereas the incidence of autoimmunity was higher in patients categorized as MB0 and MB1 groups [40].

One major difference between the Paris and the Freiburg classification is that the Paris classification calculates the class switched memory B cells by the percentage of total B cells, whilst for the Freiburg classification the memory B cells are calculated by the percentage of all peripheral blood lymphocytes. Both classifications show a correlation between the severity of disease and the proportion of switched memory B cells [41].

7.3. EUROclass Classification

EUROclass is a multicenter European trial that clasifies patients based on their percentage of CD19 B cells. Thus, patients with ≤1% CD19 B cells are designated as group B^- and those with a higher number of B cells (>1%) are designated as group B^+. Group B^+ is then divided into smB^- with ≤2% switched memory B cells and smB^+ with >2% of switched memory B cells groups. The smB^- patients group is further divided into group smB^-Tr^{hi} with ≥9% transitional B cells ($CD21^{int}$ $CD38^{++}$ IgM^{++}) and group smB^-Tr^{norm} with <9% transitional B cells. In addition, EUROclass distinguishes patients based on the expansion of $CD21^{low}$ B cells. Patients with ≥10% $CD21^{low}$ B cells are known as group $CD21^{low}$ and those with <10% are categorized as $CD21^{norm}$ allowing overlap between patients with the expansion of $CD21^{low}$ and transitional B cells. This classification is currently the most suitable in order to predict complications such as granulomatous disease, lymphadenopathy, and splenomegaly in CVID patients. Based on this classification, CVID patients with a severe decreased smB are associated with a higher risk for splenomegaly and granulomatous disease. Moreover, CVID patients with splenomegaly are associated with an expansion of $CD21^{low}$ B cells while lymphadenopathy is significantly linked with transitional B-cell expansion [41]. In a recent study, we also confirmed an association between the presence of smB^+CD21^{low} and splenomegaly in CVID patients [8]

7.4. B cell pattern classification

According to this classification, patients are divided into five distinct groups based on their B cells subsets. Patients in group 1, show decreased numbers of transitional B-cells along with a reduction of memory B-cells. Group 2 patients have a reduced number of transitional B-cells, naive, marginal zone-

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like and memory B cells. Patients with a reduction of both marginal zone-like and memory B-cells are classified in group 3, whilst in group 4, patients show only decreased memory B-cells. Finally, patients in group 5 show normal marginal zone-like and memory B-cells in combination with a reduction in plasmablasts count.

7.5. Other immunologic classification

Light chains are physiologically expressed in slight excess resulting in free light chains detectable in serum (sFLC). Detection of sFLCs in CVID by Hanitsch et al. [157] showed that 37% had normal kappa and lambda chains (κ^+/λ^+), 12% reduced kappa chains (κ^-/λ^+), 5% reduced lambda chains (κ^+/λ^-), and in 46% reduction of both chains (κ^-/λ^-). Of note, there was a clinical correlation between κ^-/λ^- sFLCs phenotype and the development of recurrent pneumonia, bronchiectasis and lymphoproliferative disease. Moreover, there is a classification based on clinical manifestation proposed by Chapel H et al. in 2008. According to this classification, patients are divided into 5 distinct clinical phenotypes including no complications, autoimmunity, polyclonal lymphocytic infiltration, enteropathy, and lymphoid malignancy [103].

8. Management

As mentioned above, hypogammaglobulinemia is the hallmark of CVID and Ig replacement therapy is the most important therapeutic intervention [158]. Indeed, Ig replacement therapy decreases the rates of recurrent and severe infections and consequent hospitalizations [158]. Some patients with comorbidities, protein losing conditions, as well as pregnant patients, may require dose adjustment [159, 160]. In addition, prophylactic and therapeutic antibiotics and complementary vaccinations with inactive antigens are recommended in these patients [158]. Vaccination in a subgroup of CVID patients with post-germinal center B-cell pattern is effective both in boosting humoral and cellular immunity [161]. As hepatic and renal dysfunctions are not uncommon in CVID patients, therapeutic modalities should be adjusted when necessary [162].

Furthermore, since CVID patients are prone to non-infectious complications such as autoimmunity, the caring physician should continuously monitor for the occurrence of these manifestations. In addition, specific treatment of autoimmune complications with immune modulation might be indicated. Herein, it should be noted that treating physician may consider immunosuppressive drugs such as Abatacept, Infliximab and Rituximab in the treatment of autoimmune manifestations of CVID patients with *CTLA-4* and *LRBA* mutations or mTOR inhibitors especially in patients with PI3K signaling defect [163].

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HSCT a potentially curative treatment approach has been performed in some cases of CVID with mixed results. Currently, HSCT only being advised in extremely severe CVID cases mostly associated with cellular immune defects and therapy resistant autoimmunity because of high mortality in spite of being beneficial in most surviving patients. However, it may become a potential treatment for specific CVID genetically characterized forms [10].

9. Conclusion

In this article, we reviewed the epidemiology, clinical manifestations, pathogenesis, diagnosis, classifications and management of CVID patients. This review provides a comprehensive overview of CVID but it is noteworthy that to date many highly relevant questions remain unanswered. This is likely due to the extreme heterogeneity of this disorder. The establishment of generally accepted diagnostic criteria, as well as the introduction of patients according to these criteria in international registries steps mandatory first steps in order to design and perform meaningful studies. The identification of patients with monogenetic defects within the CVID cohorts has helped to increase our understanding of the pathogenesis of this complex disorder and might enable us to offer targeted treatment strategies beyond Ig replacement in the future.

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Conflicts of Interest

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References

1. Aghamohammadi A, Allahverdi A, Abolhassani H, Moazzami K, Alizadeh H, Gharagozlou M, Kalantari N, Sajedi V, Shafiei A, Parvaneh N, Mohammadpour M, Karimi N, Sadaghiani MS, Rezaei N. Comparison of pulmonary diseases in common variable immunodeficiency and X-linked agammaglobulinaemia. Respirology. 2010;15:289-95.
2. Aghamohammadi A, Abolhassani H, Moazzami K, Parvaneh N, Rezaei N. Correlation between common variable immunodeficiency clinical phenotypes and parental consanguinity in children and adults. Journal of investigational allergology & clinical immunology. 2010;20:372-9.
3. Bonilla FA, Barlan I, Chapel H, Costa-Carvalho BT, Cunningham-Rundles C, de la Morena MT, Espinosa-Rosales FJ, Hammarstrom L, Nonoyama S, Quinti I, Routes JM, Tang ML, Warnatz K. International Consensus Document (ICON): Common Variable Immunodeficiency Disorders. The journal of allergy and clinical immunology In practice. 2016;4:38-59.
4. Abolhassani H, Aghamohammadi A, Fang M, Rezaei N, Jiang C, Liu X, Pan-Hammarstrom Q, Hammarstrom L. Clinical implications of systematic phenotyping and exome sequencing in patients with primary antibody deficiency. Genetics in medicine : official journal of the American College of Medical Genetics. 2018.
5. Azizi G, Rezaei N, Kiaee F, Tavakolinia N, Yazdani R, Mirshafiey A, Aghamohammadi A. T-Cell Abnormalities in Common Variable Immunodeficiency. Journal of investigational allergology & clinical immunology. 2016;26:233-43.
6. Sharifi L, Mirshafiey A, Rezaei N, Azizi G, Magaji Hamid K, Amirzargar AA, Asgardoon MH, Aghamohammadi A. The role of toll-like receptors in B-cell development and immunopathogenesis of common variable immunodeficiency. Expert Rev Clin Immunol. 2016;12:195-207.
7. Sharifi L, Tavakolinia N, Kiaee F, Rezaei N, Mohsenzadegan M, Azizi G, Yazdani R, Shariat M, Mirshafiey A, Aghamohammadi A. A Review on Defects of Dendritic Cells in Common Variable Immunodeficiency. Endocr Metab Immune Disord Drug Targets. 2017;17:100-13.
8. Yazdani R, Seify R, Ganjalikhani-Hakemi M, Abolhassani H, Eskandari N, Golsaz-Shirazi F, Ansaripour B, Salehi E, Azizi G, Rezaei N, Aghamohammadi A. Comparison of various classifications for patients with common variable immunodeficiency (CVID) using measurement of B-cell subsets. Allergologia et immunopathologia. 2017;45:183-92.
9. Gathmann B, Mahlaoui N, Ceredih, Gerard L, Oksenhendler E, Warnatz K, Schulze I, Kindle G, Kuijpers TW, Dutch WID, van Beem RT, Guzman D, Workman S, Soler-Palacin P, De Gracia J, Witte T, Schmidt RE, Litzman J, Hlavackova E, Thon V, Borte M, Borte S, Kumararatne D, Feighery C, Longhurst H, Helbert M, Szaflarska A, Sediva A, Belohradsky BH, Jones A, Baumann U, Meyts I, Kutukculer N, Wagstrom P, Galal NM, Roesler J, Farmaki E, Zinovieva N, Ciznar P, Papadopoulou-Alataki E, Bienemann K, Velbri S, Panahloo Z, Grimbacher B, European Society for Immunodeficiencies Registry Working P. Clinical picture and treatment of 2212 patients with common variable immunodeficiency. J Allergy Clin Immunol. 2014;134:116-26.
10. Wehr C, Gennery AR, Lindemans C, Schulz A, Hoenig M, Marks R, Recher M, Gruhn B, Holbro A, Heijnen I, Meyer D, Grigoleit G, Einsele H, Baumann U, Witte T, Sykora KW, Goldacker S, Regairaz L, Aksoylar S, Ardeniz O, Zecca M, Zdziarski P, Meyts I, Matthes-Martin S, Imai K, Kamae C, Fielding A, Seneviratne S, Mahlaoui N, Slatter MA, Gungor T, Arkwright PD, van Montfrans J, Sullivan KE, Grimbacher B, Cant A, Peter HH, Finke J, Gaspar HB, Warnatz K, Rizzi M. Multicenter experience in hematopoietic stem cell transplantation for serious complications of common variable immunodeficiency. J Allergy Clin Immunol. 2015;135:988-97.

doi: 10.18176/jiaci.0388

11. Cunningham-Rundles C, Maglione PJ. Common variable immunodeficiency. J Allergy Clin Immunol. 2012;129:1425-6.
12. Modell V, Orange JS, Quinn J, Modell F. Global report on primary immunodeficiencies: 2018 update from the Jeffrey Modell Centers Network on disease classification, regional trends, treatment modalities, and physician reported outcomes. Immunologic research. 2018.
13. Shillitoe B, Bangs C, Guzman D, Gennery AR, Longhurst HJ, Slatter M, Edgar DM, Thomas M, Worth A, Huissoon A, Arkwright PD, Jolles S, Bourne H, Alachkar H, Savic S, Kumararatne DS, Patel S, Baxendale H, Noorani S, Yong PFK, Waruiru C, Pavaladurai V, Kelleher P, Herriot R, Bernatonienne J, Bhole M, Steele C, Hayman G, Richter A, Gompels M, Chopra C, Garcez T, Buckland M. The United Kingdom Primary Immune Deficiency (UKPID) registry 2012 to 2017. Clin Exp Immunol. 2018;192:284-91.
14. Sanchez LA, Maggadottir SM, Pantell MS, Lugar P, Rundles CC, Sullivan KE, Consortium U. Two Sides of the Same Coin: Pediatric-Onset and Adult-Onset Common Variable Immune Deficiency. Journal of clinical immunology. 2017;37:592-602.
15. Yazdani R, Abolhassani H, Kiaee F, Habibi S, Azizi G, Tavakol M, Chavoshzadeh Z, Mahdaviani SA, Momen T, Gharagozlou M, Movahedi M, Hamidieh AA, Behniafard N, Nabavi M, Bemanian MH, Arshi S, Molatefi R, Sherkat R, Shirkani A, Amin R, Aleyasin S, Faridhosseini R, Jabbari-Azad F, Mohammadzadeh I, Ghaffari J, Shafiei A, Kalantari A, Mansouri M, Mesdaghi M, Babaie D, Ahanchian H, Khoshkhui M, Soheili H, Eslamian MH, Cheraghi T, Dabbaghzadeh S, Tavassoli M, Kalmarzi RN, Mortazavi SH, Kashef S, Esmaeilzadeh H, Tafaroji J, Khalili A, Zandieh F, Sadeghi-Shabestari M, Darougar S, Behmanesh F, Akbari H, Zandkarimi M, Abolnezhadian F, Fayezi A, Moghtaderi M, Ahmadiafshar A, Shakerian B, Sajedi V, Taghvaei B, Safari M, Heidarzadeh M, Ghalebaghi B, Fathi SM, Darabi B, Bazregari S, Bazargan N, Fallahpour M, Khayatzadeh A, Javahertrash N, Bashardoust B, Zamani M, Mohsenzadeh A, Ebrahimi S, Sharafian S, Vosughimotlagh A, Tafakoridelbari M, Rahim M, Ashournia P, Razaghian A, Rezaei A, Samavat A, Mamishi S, Khazaei HA, Mohammadi J, Negahdari B, Parvaneh N, Rezaei N, Lougaris V, Giliani S, Plebani A, Ochs HD, Hammarstrom L, Aghamohammadi A. Comparison of Common Monogenic Defects in a Large Predominantly Antibody Deficiency Cohort. The journal of allergy and clinical immunology In practice. 2018.
16. Rae W. Indications to Epigenetic Dysfunction in the Pathogenesis of Common Variable Immunodeficiency. Archivum immunologiae et therapiae experimentalis. 2017;65:101-10.
17. Rodriguez-Cortez VC, Del Pino-Molina L, Rodriguez-Ubreva J, Ciudad L, Gomez-Cabrero D, Company C, Urquiza JM, Tegner J, Rodriguez-Gallego C, Lopez-Granados E, Ballestar E. Monozygotic twins discordant for common variable immunodeficiency reveal impaired DNA demethylation during naive-to-memory B-cell transition. Nature communications. 2015;6:7335.
18. Martinez-Gallo M, Radigan L, Almejun MB, Martinez-Pomar N, Matamoros N, Cunningham-Rundles C. TACI mutations and impaired B-cell function in subjects with CVID and healthy heterozygotes. J Allergy Clin Immunol. 2013;131:468-76.
19. Kutukculer N, Gulez N, Karaca NE, Aksu G, Berdeli A. Three different classifications, B lymphocyte subpopulations, TNFRSF13B (TACI), TNFRSF13C (BAFF-R), TNFSF13 (APRIL) gene mutations, CTLA-4 and ICOS gene polymorphisms in Turkish patients with common variable immunodeficiency. Journal of clinical immunology. 2012;32:1165-79.
20. Romberg N, Chamberlain N, Saadoun D, Gentile M, Kinnunen T, Ng YS, Virdee M, Menard L, Cantaert T, Morbach H, Rachid R, Martinez-Pomar N, Matamoros N, Geha R, Grimbacher B, Cerutti A, Cunningham-Rundles C, Meffre E. CVID-associated TACI mutations affect autoreactive B cell selection and activation. The Journal of clinical investigation. 2013;123:4283-93.
21. Bousfiha A, Jeddane L, Picard C, Ailal F, Bobby Gaspar H, Al-Herz W, Chatila T, Crow YJ, Cunningham-Rundles C, Etzioni A, Franco JL, Holland SM, Klein C, Morio T, Ochs HD, Oksenhendler E,

doi: 10.18176/jiaci.0388

Puck J, Tang MLK, Tangye SG, Torgerson TR, Casanova JL, Sullivan KE. The 2017 IUIS Phenotypic Classification for Primary Immunodeficiencies. Journal of clinical immunology. 2018;38:129-43.
22. Tallmadge RL, Shen L, Tseng CT, Miller SC, Barry J, Felippe MJ. Bone marrow transcriptome and epigenome profiles of equine common variable immunodeficiency patients unveil block of B lymphocyte differentiation. Clinical immunology (Orlando, Fla). 2015;160:261-76.
23. Kramer NJ, Wang WL, Reyes EY, Kumar B, Chen CC, Ramakrishna C, Cantin EM, Vonderfecht SL, Taganov KD, Chau N, Boldin MP. Altered lymphopoiesis and immunodeficiency in miR-142 null mice. 2015;125:3720-30.
24. Heo JB, Lee YS, Sung S. Epigenetic regulation by long noncoding RNAs in plants. Chromosome research : an international journal on the molecular, supramolecular and evolutionary aspects of chromosome biology. 2013;21:685-93.
25. Eden S, Cedar H. Role of DNA methylation in the regulation of transcription. Current opinion in genetics & development. 1994;4:255-9.
26. Zhou H, Hu H, Lai M. Non-coding RNAs and their epigenetic regulatory mechanisms. Biology of the cell. 2010;102:645-55.
27. Rodriguez A, Vigorito E, Clare S, Warren MV, Couttet P, Soond DR, van Dongen S, Grocock RJ, Das PP, Miska EA, Vetrie D, Okkenhaug K, Enright AJ, Dougan G, Turner M, Bradley A. Requirement of bic/microRNA-155 for normal immune function. Science (New York, NY). 2007;316:608-11.
28. Lindsley AW, Saal HM, Burrow TA, Hopkin RJ, Shchelochkov O, Khandelwal P, Xie C, Bleesing J, Filipovich L, Risma K, Assa'ad AH, Roehrs PA, Bernstein JA. Defects of B-cell terminal differentiation in patients with type-1 Kabuki syndrome. J Allergy Clin Immunol. 2016;137:179-87.e10.
29. Belkaid Y, Hand TW. Role of the microbiota in immunity and inflammation. Cell. 2014;157:121-41.
30. Brenchley JM, Price DA, Schacker TW, Asher TE, Silvestri G, Rao S, Kazzaz Z, Bornstein E, Lambotte O, Altmann D, Blazar BR, Rodriguez B, Teixeira-Johnson L, Landay A, Martin JN, Hecht FM, Picker LJ, Lederman MM, Deeks SG, Douek DC. Microbial translocation is a cause of systemic immune activation in chronic HIV infection. Nature medicine. 2006;12:1365-71.
31. Xavier RJ, Podolsky DK. Unravelling the pathogenesis of inflammatory bowel disease. Nature. 2007;448:427-34.
32. Jorgensen SF, Troseid M, Kummen M, Anmarkrud JA, Michelsen AE, Osnes LT, Holm K, Hoivik ML, Rashidi A, Dahl CP, Vesterhus M, Halvorsen B, Mollnes TE, Berge RK, Moum B, Lundin KE, Fevang B, Ueland T, Karlsen TH, Aukrust P, Hov JR. Altered gut microbiota profile in common variable immunodeficiency associates with levels of lipopolysaccharide and markers of systemic immune activation. Mucosal immunology. 2016;9:1455-65.
33. Weller S, Faili A, Garcia C, Braun MC, Le Deist FF, de Saint Basile GG, Hermine O, Fischer A, Reynaud CA, Weill JC. CD40-CD40L independent Ig gene hypermutation suggests a second B cell diversification pathway in humans. Proceedings of the National Academy of Sciences of the United States of America. 2001;98:1166-70.
34. Carsetti R, Rosado MM, Donnanno S, Guazzi V, Soresina A, Meini A, Plebani A, Aiuti F, Quinti I. The loss of IgM memory B cells correlates with clinical disease in common variable immunodeficiency. J Allergy Clin Immunol. 2005;115:412-7.
35. Ahn S, Cunningham-Rundles C. Role of B cells in common variable immune deficiency. Expert Rev Clin Immunol. 2009;5:557-64.
36. Warnatz K, Schlesier M. Flowcytometric phenotyping of common variable immunodeficiency. Cytometry Part B, Clinical cytometry. 2008;74:261-71.
37. Ganjalikhani-Hakemi M, Yazdani R, Esmaeili M, Abolhassani H, Rae W, Azizi G, Dizaji MZ, Shaghaghi M, Rezaei A, Abbasi-Rad F, Afshar-Qasemloo S, Mohammadi S, Rezaei N, Aghamohammadi A.

doi: 10.18176/jiaci.0388

Role of Apoptosis in the Pathogenesis of Common Variable Immunodeficiency (CVID). Endocr Metab Immune Disord Drug Targets. 2017;17:332-40.
38. Yazdani R, Fatholahi M, Ganjalikhani-Hakemi M, Abolhassani H, Azizi G, Hamid KM, Rezaei N, Aghamohammadi A. Role of apoptosis in common variable immunodeficiency and selective immunoglobulin A deficiency. Molecular immunology. 2016;71:1-9.
39. Warnatz K, Denz A, Drager R, Braun M, Groth C, Wolff-Vorbeck G, Eibel H, Schlesier M, Peter HH. Severe deficiency of switched memory B cells (CD27(+)IgM(-)IgD(-)) in subgroups of patients with common variable immunodeficiency: a new approach to classify a heterogeneous disease. Blood. 2002;99:1544-51.
40. Piqueras B, Lavenu-Bombled C, Galicier L, Bergeron-van der Cruyssen F, Mouthon L, Chevret S, Debre P, Schmitt C, Oksenhendler E. Common variable immunodeficiency patient classification based on impaired B cell memory differentiation correlates with clinical aspects. Journal of clinical immunology. 2003;23:385-400.
41. Wehr C, Kivioja T, Schmitt C, Ferry B, Witte T, Eren E, Vlkova M, Hernandez M, Detkova D, Bos PR, Poerksen G, von Bernuth H, Baumann U, Goldacker S, Gutenberger S, Schlesier M, Bergeron-van der Cruyssen F, Le Garff M, Debre P, Jacobs R, Jones J, Bateman E, Litzman J, van Hagen PM, Plebani A, Schmidt RE, Thon V, Quinti I, Espanol T, Webster AD, Chapel H, Vihinen M, Oksenhendler E, Peter HH, Warnatz K. The EUROclass trial: defining subgroups in common variable immunodeficiency. Blood. 2008;111:77-85.
42. Cuss AK, Avery DT, Cannons JL, Yu LJ, Nichols KE, Shaw PJ, Tangye SG. Expansion of functionally immature transitional B cells is associated with human-immunodeficient states characterized by impaired humoral immunity. Journal of immunology (Baltimore, Md : 1950). 2006;176:1506-16.
43. Warnatz K, Salzer U, Rizzi M, Fischer B, Gutenberger S, Bohm J, Kienzler AK, Pan-Hammarstrom Q, Hammarstrom L, Rakhmanov M, Schlesier M, Grimbacher B, Peter HH, Eibel H. B-cell activating factor receptor deficiency is associated with an adult-onset antibody deficiency syndrome in humans. Proceedings of the National Academy of Sciences of the United States of America. 2009;106:13945-50.
44. Unger S, Seidl M, van Schouwenburg P, Rakhmanov M, Bulashevska A, Frede N, Grimbacher B, Pfeiffer J, Schrenk K, Munoz L, Hanitsch L, Stumpf I, Kaiser F, Hausmann O, Kollert F, Goldacker S, van der Burg M, Keller B, Warnatz K. TH1 phenotype of T follicular helper cells indicates an IFNgamma-associated immune dysregulation in CD21low CVID patients. J Allergy Clin Immunol. 2017.
45. Taraldsrud E, Aukrust P, Jorgensen S, Lingjaerde OC, Olweus J, Myklebust JH, Fevang B. Patterns of constitutively phosphorylated kinases in B cells are associated with disease severity in common variable immunodeficiency. Clinical immunology (Orlando, Fla). 2017;175:69-74.
46. Giovannetti A, Pierdominici M, Mazzetta F, Marziali M, Renzi C, Mileo AM, De Felice M, Mora B, Esposito A, Carello R, Pizzuti A, Paggi MG, Paganelli R, Malorni W, Aiuti F. Unravelling the complexity of T cell abnormalities in common variable immunodeficiency. Journal of immunology (Baltimore, Md : 1950). 2007;178:3932-43.
47. Vlkova M, Ticha O, Nechvatalova J, Kalina T, Litzman J, Mauri C, Blair PA. Regulatory B cells in CVID patients fail to suppress multifunctional IFN-gamma+ TNF-alpha+ CD4+ T cells differentiation. Clinical immunology (Orlando, Fla). 2015;160:292-300.
48. Bateman EA, Ayers L, Sadler R, Lucas M, Roberts C, Woods A, Packwood K, Burden J, Harrison D, Kaenzig N, Lee M, Chapel HM, Ferry BL. T cell phenotypes in patients with common variable immunodeficiency disorders: associations with clinical phenotypes in comparison with other groups with recurrent infections. Clin Exp Immunol. 2012;170:202-11.
49. Oraei M, Aghamohammadi A, Rezaei N, Bidad K, Gheflati Z, Amirkhani A, Abolhassani H, Massoud A. Naive CD4+ T cells and recent thymic emigrants in common variable immunodeficiency. Journal of investigational allergology & clinical immunology. 2012;22:160-7.

doi: 10.18176/jiaci.0388

50. Rezaei N, Haji-Molla-Hoseini M, Aghamohammadi A, Pourfathollah AA, Moghtadaie M, Pourpak Z. Increased serum levels of soluble CD30 in patients with common variable immunodeficiency and its clinical implications. Journal of clinical immunology. 2008;28:78-84.
51. North ME, Ivory K, Funauchi M, Webster AD, Lane AC, Farrant J. Intracellular cytokine production by human CD4+ and CD8+ T cells from normal and immunodeficient donors using directly conjugated anti-cytokine antibodies and three-colour flow cytometry. Clin Exp Immunol. 1996;105:517-22.
52. North ME, Webster AD, Farrant J. Primary defect in CD8+ lymphocytes in the antibody deficiency disease (common variable immunodeficiency): abnormalities in intracellular production of interferon-gamma (IFN-gamma) in CD28+ ('cytotoxic') and CD28- ('suppressor') CD8+ subsets. Clin Exp Immunol. 1998;111:70-5.
53. Barbosa RR, Silva SP, Silva SL, Melo AC, Pedro E, Barbosa MP, Pereira-Santos MC, Victorino RM, Sousa AE. Primary B-cell deficiencies reveal a link between human IL-17-producing CD4 T-cell homeostasis and B-cell differentiation. PloS one. 2011;6:e22848.
54. Ganjalikhani-Hakemi M, Yazdani R, Sherkat R, Homayouni V, Masjedi M, Hosseini M. Evaluation of the T helper 17 cell specific genes and the innate lymphoid cells counts in the peripheral blood of patients with the common variable immunodeficiency. Journal of research in medical sciences : the official journal of Isfahan University of Medical Sciences. 2014;19:S30-5.
55. Coraglia A, Galassi N, Fernandez Romero DS, Juri MC, Felippo M, Malbran A, de Bracco MM. Common Variable Immunodeficiency and Circulating TFH. Journal of immunology research. 2016;2016:4951587.
56. Cunill V, Clemente A, Lanio N, Barcelo C, Andreu V, Pons J, Ferrer JM. Follicular T Cells from smB(-) Common Variable Immunodeficiency Patients Are Skewed Toward a Th1 Phenotype. Frontiers in immunology. 2017;8:174.
57. Bauquet AT, Jin H, Paterson AM, Mitsdoerffer M, Ho IC, Sharpe AH, Kuchroo VK. The costimulatory molecule ICOS regulates the expression of c-Maf and IL-21 in the development of follicular T helper cells and TH-17 cells. Nature immunology. 2009;10:167-75.
58. Bossaller L, Burger J, Draeger R, Grimbacher B, Knoth R, Plebani A, Durandy A, Baumann U, Schlesier M, Welcher AA, Peter HH, Warnatz K. ICOS deficiency is associated with a severe reduction of CXCR5+CD4 germinal center Th cells. Journal of immunology (Baltimore, Md : 1950). 2006;177:4927-32.
59. Pellerin L, Jenks JA, Begin P, Bacchetta R, Nadeau KC. Regulatory T cells and their roles in immune dysregulation and allergy. Immunologic research. 2014;58:358-68.
60. Kutukculer N, Azarsiz E, Aksu G, Karaca NE. CD4+CD25+Foxp3+ T regulatory cells, Th1 (CCR5, IL-2, IFN-gamma) and Th2 (CCR4, IL-4, Il-13) type chemokine receptors and intracellular cytokines in children with common variable immunodeficiency. International journal of immunopathology and pharmacology. 2016;29:241-51.
61. Arandi N, Mirshafiey A, Abolhassani H, Jeddi-Tehrani M, Edalat R, Sadeghi B, Shaghaghi M, Aghamohammadi A. Frequency and expression of inhibitory markers of CD4(+) CD25(+) FOXP3(+) regulatory T cells in patients with common variable immunodeficiency. Scandinavian journal of immunology. 2013;77:405-12.
62. Genre J, Errante PR, Kokron CM, Toledo-Barros M, Camara NO, Rizzo LV. Reduced frequency of CD4(+)CD25(HIGH)FOXP3(+) cells and diminished FOXP3 expression in patients with Common Variable Immunodeficiency: a link to autoimmunity? Clinical immunology (Orlando, Fla). 2009;132:215-21.
63. Yu GP, Chiang D, Song SJ, Hoyte EG, Huang J, Vanishsarn C, Nadeau KC. Regulatory T cell dysfunction in subjects with common variable immunodeficiency complicated by autoimmune disease. Clinical immunology (Orlando, Fla). 2009;131:240-53.

doi: 10.18176/jiaci.0388

64. Arumugakani G, Wood PM, Carter CR. Frequency of Treg cells is reduced in CVID patients with autoimmunity and splenomegaly and is associated with expanded CD21lo B lymphocytes. Journal of clinical immunology. 2010;30:292-300.
65. Carbone J, Sarmiento E, Micheloud D, Rodriguez-Molina J, Fernandez-Cruz E. Elevated levels of activated CD4 T cells in common variable immunodeficiency: association with clinical findings. Allergologia et immunopathologia. 2006;34:131-5.
66. Viallard JF, Ruiz C, Guillet M, Pellegrin JL, Moreau JF. Perturbations of the CD8(+) T-cell repertoire in CVID patients with complications. Results in immunology. 2013;3:122-8.
67. Carter CR, Aravind G, Smalle NL, Cole JY, Savic S, Wood PM. CVID patients with autoimmunity have elevated T cell expression of granzyme B and HLA-DR and reduced levels of Treg cells. Journal of clinical pathology. 2013;66:146-50.
68. Viallard JF, Blanco P, Andre M, Etienne G, Liferman F, Neau D, Vidal E, Moreau JF, Pellegrin JL. CD8+HLA-DR+ T lymphocytes are increased in common variable immunodeficiency patients with impaired memory B-cell differentiation. Clinical immunology (Orlando, Fla). 2006;119:51-8.
69. Nechvatalova J, Pavlik T, Litzman J, Vlkova M. Terminally differentiated memory T cells are increased in patients with common variable immunodeficiency and selective IgA deficiency. Central-European journal of immunology. 2017;42:244-51.
70. Paquin-Proulx D, Barsotti NS, Santos BA, Marinho AK, Kokron CM, Carvalho KI, Barros MT, Kalil J, Nixon DF, Kallas EG. Inversion of the Vdelta1 to Vdelta2 gammadelta T cell ratio in CVID is not restored by IVIg and is associated with immune activation and exhaustion. Medicine. 2016;95:e4304.
71. Bayry J, Lacroix-Desmazes S, Kazatchkine MD, Galicier L, Lepelletier Y, Webster D, Levy Y, Eibl MM, Oksenhendler E, Hermine O, Kaveri SV. Common variable immunodeficiency is associated with defective functions of dendritic cells. Blood. 2004;104:2441-3.
72. Cunningham-Rundles C, Radigan L. Deficient IL-12 and dendritic cell function in common variable immune deficiency. Clinical immunology (Orlando, Fla). 2005;115:147-53.
73. Cunningham-Rundles C, Radigan L, Knight AK, Zhang L, Bauer L, Nakazawa A. TLR9 activation is defective in common variable immune deficiency. Journal of immunology (Baltimore, Md : 1950). 2006;176:1978-87.
74. Taraldsrud E, Fevang B, Aukrust P, Beiske KH, Floisand Y, Froland S, Rollag H, Olweus J. Common variable immunodeficiency revisited: normal generation of naturally occurring dendritic cells that respond to Toll-like receptors 7 and 9. Clin Exp Immunol. 2014;175:439-48.
75. Aukrust P, Muller F, Froland SS. Enhanced generation of reactive oxygen species in monocytes from patients with common variable immunodeficiency. Clin Exp Immunol. 1994;97:232-8.
76. Aukrust P, Lien E, Kristoffersen AK, Muller F, Haug CJ, Espevik T, Froland SS. Persistent activation of the tumor necrosis factor system in a subgroup of patients with common variable immunodeficiency--possible immunologic and clinical consequences. Blood. 1996;87:674-81.
77. Cambronero R, Sewell WA, North ME, Webster AD, Farrant J. Up-regulation of IL-12 in monocytes: a fundamental defect in common variable immunodeficiency. Journal of immunology (Baltimore, Md : 1950). 2000;164:488-94.
78. Scott-Taylor TH, Whiting K, Pettengell R, Webster DA. Enhanced formation of giant cells in common variable immunodeficiency: Relation to granulomatous disease. Clinical immunology (Orlando, Fla). 2017;175:1-9.
79. Yazdani R, Sharifi M, Shirvan AS, Azizi G, Ganjalikhani-Hakemi M. Characteristics of innate lymphoid cells (ILCs) and their role in immunological disorders (an update). Cellular immunology. 2015;298:66-76.
80. Cols M, Rahman A, Maglione PJ, Garcia-Carmona Y, Simchoni N, Ko HB, Radigan L, Cerutti A, Blankenship D, Pascual V, Cunningham-Rundles C. Expansion of inflammatory innate lymphoid cells in patients with common variable immune deficiency. J Allergy Clin Immunol. 2016;137:1206-15.e1-6.

doi: 10.18176/jiaci.0388

81. Aspalter RM, Sewell WA, Dolman K, Farrant J, Webster AD. Deficiency in circulating natural killer (NK) cell subsets in common variable immunodeficiency and X-linked agammaglobulinaemia. Clin Exp Immunol. 2000;121:506-14.
82. Ebbo M, Gérard L, Carpentier S, Vély F, Cypowyj S, Farnarier C, Vince N, Malphettes M, Fieschi C, Oksenhendler E, Schleinitz N, Vivier E. Low Circulating Natural Killer Cell Counts are Associated With Severe Disease in Patients With Common Variable Immunodeficiency. EBioMedicine. 2016;6:222-30.
83. Kutukculer N, Azarsiz E, Karaca NE, Ulusoy E, Koturoglu G, Aksu G. A Clinical and Laboratory Approach to the Evaluation of Innate Immunity in Pediatric CVID Patients. Frontiers in immunology. 2015;6:145.
84. Geier CB, Kraupp S, Bra D, Eibl MM, Farmer JR, Csomos K, Walter JE, Wolf HM. Reduced numbers of circulating group 2 innate lymphoid cells in patients with common variable immunodeficiency. European journal of immunology. 2017;47:1959-69.
85. Carvalho KI, Melo KM, Bruno FR, Snyder-Cappione JE, Nixon DF, Costa-Carvalho BT, Kallas EG. Skewed distribution of circulating activated natural killer T (NKT) cells in patients with common variable immunodeficiency disorders (CVID). PloS one. 2010;5.
86. Erazo-Borras LV, Alvarez-Alvarez JA, Perez-Romero CA, Orrego-Arango JC, Franco-Restrepo JL, Trujillo-Vargas CM. Skewed Invariant Natural Killer T (iNKT) Cells, Impaired iNKT:B Cell Help and Decreased SAP Expression in Blood Lymphocytes from Patients with Common Variable Immunodeficiency. Scandinavian journal of immunology. 2017;86:171-8.
87. Patuzzo G, Barbieri A, Tinazzi E, Veneri D, Argentino G, Moretta F, Puccetti A, Lunardi C. Autoimmunity and infection in common variable immunodeficiency (CVID). Autoimmun Rev. 2016;15:877-82.
88. Yazdani R, Abolhassani H, Asgardoon M, Shaghaghi M, Modaresi M, Azizi G, Aghamohammadi A. Infectious and Noninfectious Pulmonary Complications in Patients With Primary Immunodeficiency Disorders. Journal of investigational allergology & clinical immunology. 2017;27:213-24.
89. Quinti I, Soresina A, Guerra A, Rondelli R, Spadaro G, Agostini C, Milito C, Trombetta AC, Visentini M, Martini H, Plebani A, Fiorilli M, Investigators IP. Effectiveness of immunoglobulin replacement therapy on clinical outcome in patients with primary antibody deficiencies: results from a multicenter prospective cohort study. Journal of clinical immunology. 2011;31:315-22.
90. Hampson FA, Chandra A, Screaton NJ, Condliffe A, Kumararatne DS, Exley AR, Babar JL. Respiratory disease in common variable immunodeficiency and other primary immunodeficiency disorders. Clinical radiology. 2012;67:587-95.
91. Kainulainen L, Vuorinen T, Rantakokko-Jalava K, Osterback R, Ruuskanen O. Recurrent and persistent respiratory tract viral infections in patients with primary hypogammaglobulinemia. J Allergy Clin Immunol. 2010;126:120-6.
92. Pasteur MC, Bilton D, Hill AT, British Thoracic Society Bronchiectasis non CFGG. British Thoracic Society guideline for non-CF bronchiectasis. Thorax. 2010;65 Suppl 1:i1-58.
93. Verma N, Grimbacher B, Hurst JR. Lung disease in primary antibody deficiency. Lancet Respir Med. 2015;3:651-60.
94. Oksenhendler E, Gerard L, Fieschi C, Malphettes M, Mouillot G, Jaussaud R, Viallard JF, Gardembas M, Galicier L, Schleinitz N, Suarez F, Soulas-Sprauel P, Hachulla E, Jaccard A, Gardeur A, Theodorou I, Rabian C, Debre P, Group DS. Infections in 252 patients with common variable immunodeficiency. Clin Infect Dis. 2008;46:1547-54.
95. Malamut G, Verkarre V, Suarez F, Viallard JF, Lascaux AS, Cosnes J, Bouhnik Y, Lambotte O, Bechade D, Ziol M, Lavergne A, Hermine O, Cerf-Bensussan N, Cellier C. The enteropathy associated with common variable immunodeficiency: the delineated frontiers with celiac disease. The American journal of gastroenterology. 2010;105:2262-75.

doi: 10.18176/jiaci.0388

96. Daniels JA, Lederman HM, Maitra A, Montgomery EA. Gastrointestinal tract pathology in patients with common variable immunodeficiency (CVID): a clinicopathologic study and review. Am J Surg Pathol. 2007;31:1800-12.
97. Maarschalk-Ellerbroek LJ, Oldenburg B, Mombers IM, Hoepelman AI, Brosens LA, Offerhaus GJ, Ellerbroek PM. Outcome of screening endoscopy in common variable immunodeficiency disorder and X-linked agammaglobulinemia. Endoscopy. 2013;45:320-3.
98. Everhart JE, Kruszon-Moran D, Perez-Perez GI, Tralka TS, McQuillan G. Seroprevalence and ethnic differences in Helicobacter pylori infection among adults in the United States. J Infect Dis. 2000;181:1359-63.
99. Desar IM, van Deuren M, Sprong T, Jansen JB, Namavar F, Vandenbroucke-Grauls CM, van der Meer JW. Serum bactericidal activity against Helicobacter pylori in patients with hypogammaglobulinaemia. Clin Exp Immunol. 2009;156:434-9.
100. Chapel H, Cunningham-Rundles C. Update in understanding common variable immunodeficiency disorders (CVIDs) and the management of patients with these conditions. British journal of haematology. 2009;145:709-27.
101. Desjardins M, Beland M, Dembele M, Lejtenyi D, Drolet JP, Lemire M, Tsoukas C, Ben-Shoshan M, Noya FJD, Alizadehfar R, McCusker CT, Mazer BD. Modulation of the Interleukin-21 Pathway with Interleukin-4 Distinguishes Common Variable Immunodeficiency Patients with More Non-infectious Clinical Complications. Journal of clinical immunology. 2018;38:45-55.
102. Sarmiento E, Mora R, Rodriguez-Mahou M, Rodriguez-Molina J, Fernandez-Cruz E, Carbone J. [Autoimmune disease in primary antibody deficiencies]. Allergologia et immunopathologia. 2005;33:69-73.
103. Chapel H, Lucas M, Lee M, Bjorkander J, Webster D, Grimbacher B, Fieschi C, Thon V, Abedi MR, Hammarstrom L. Common variable immunodeficiency disorders: division into distinct clinical phenotypes. Blood. 2008;112:277-86.
104. Ramirez-Vargas N, Arablin-Oropeza SE, Mojica-Martinez D, Yamazaki-Nakashimada MA, de la Luz Garcia-Cruz M, Teran-Juarez LM, Cortes-Grimaldo RM, Torres-Lozano C, Madrigal-Beas I, Ortega-Cisneros M, Vargas-Camano ME, Staines-Boone T, Pietropaolo-Cienfuegos D, Berron-Ruiz L, Espinosa-Rosales FJ, Guevara-Cruz M, Blancas-Galicia L. Clinical and immunological features of common variable immunodeficiency in Mexican patients. Allergologia et immunopathologia. 2014;42:235-40.
105. Azizi G, Ahmadi M, Abolhassani H, Yazdani R, Mohammadi H, Mirshafiey A, Rezaei N, Aghamohammadi A. Autoimmunity in Primary Antibody Deficiencies. International archives of allergy and immunology. 2016;171:180-93.
106. Boileau J, Mouillot G, Gerard L, Carmagnat M, Rabian C, Oksenhendler E, Pasquali JL, Korganow AS, Group DS. Autoimmunity in common variable immunodeficiency: correlation with lymphocyte phenotype in the French DEFI study. J Autoimmun. 2011;36:25-32.
107. Resnick ES, Moshier EL, Godbold JH, Cunningham-Rundles C. Morbidity and mortality in common variable immune deficiency over 4 decades. Blood. 2012;119:1650-7.
108. Todoric K, Koontz JB, Mattox D, Tarrant TK. Autoimmunity in immunodeficiency. Curr Allergy Asthma Rep. 2013;13:361-70.
109. Brandt D, Gershwin ME. Common variable immune deficiency and autoimmunity. Autoimmun Rev. 2006;5:465-70.
110. Knight AK, Cunningham-Rundles C. Inflammatory and autoimmune complications of common variable immune deficiency. Autoimmun Rev. 2006;5:156-9.
111. Xiao X, Miao Q, Chang C, Gershwin ME, Ma X. Common variable immunodeficiency and autoimmunity--an inconvenient truth. Autoimmun Rev. 2014;13:858-64.
112. Karaca NE, Aksu G, Yildiz B, Gulez N, Turk B, Dereli T, Kutukculer N. Relapsing polychondritis in a child with common variable immunodeficiency. Int J Dermatol. 2009;48:525-8.

doi: 10.18176/jiaci.0388

113. Kofod-Olsen E, Jorgensen SE, Nissen SK, Westh L, Moller BK, Ostergaard L, Larsen CS, Mogensen TH. Altered fraction of regulatory B and T cells is correlated with autoimmune phenomena and splenomegaly in patients with CVID. Clinical immunology (Orlando, Fla). 2016;162:49-57.
114. Mahmoudi M, Hedayat M, Aghamohammadi A, Rezaei N. Soluble CD26 and CD30 levels in patients with common variable immunodeficiency. Journal of investigational allergology & clinical immunology. 2013;23:120-4.
115. Salek Farrokhi A, Aghamohammadi A, Pourhamdi S, Mohammadinejad P, Abolhassani H, Moazzeni SM. Evaluation of class switch recombination in B lymphocytes of patients with common variable immunodeficiency. Journal of immunological methods. 2013;394:94-9.
116. Warnatz K, Voll RE. Pathogenesis of autoimmunity in common variable immunodeficiency. Frontiers in immunology. 2012;3:210.
117. Baldovino S, Montin D, Martino S, Sciascia S, Menegatti E, Roccatello D. Common variable immunodeficiency: crossroads between infections, inflammation and autoimmunity. Autoimmun Rev. 2013;12:796-801.
118. Salavoura K, Kolialexi A, Tsangaris G, Mavrou A. Development of cancer in patients with primary immunodeficiencies. Anticancer Res. 2008;28:1263-9.
119. Mellemkjaer L, Hammarstrom L, Andersen V, Yuen J, Heilmann C, Barington T, Bjorkander J, Olsen JH. Cancer risk among patients with IgA deficiency or common variable immunodeficiency and their relatives: a combined Danish and Swedish study. Clin Exp Immunol. 2002;130:495-500.
120. Dhalla F, da Silva SP, Lucas M, Travis S, Chapel H. Review of gastric cancer risk factors in patients with common variable immunodeficiency disorders, resulting in a proposal for a surveillance programme. Clin Exp Immunol. 2011;165:1-7.
121. Cassaro M, Rugge M, Gutierrez O, Leandro G, Graham DY, Genta RM. Topographic patterns of intestinal metaplasia and gastric cancer. The American journal of gastroenterology. 2000;95:1431-8.
122. De Petris G, Dhungel BM, Chen L, Chang YH. Gastric adenocarcinoma in common variable immunodeficiency: features of cancer and associated gastritis may be characteristic of the condition. Int J Surg Pathol. 2014;22:600-6.
123. Uzzan M, Ko HM, Mehandru S, Cunningham-Rundles C. Gastrointestinal Disorders Associated with Common Variable Immune Deficiency (CVID) and Chronic Granulomatous Disease (CGD). Current gastroenterology reports. 2016;18:17.
124. Mohebbi A, Azizi G, Tavakolinia N, Abbasi F, Sayarifard F, Karimipour M, Kiaee F, Yazdani R, Ebrahimi SS, Ebrahimi M, Rafiemanesh H, Tafaroji J, Ziaee V, Abolhassani H, Aghamohammadi A. Comparison of Bone Mineral Density in Common Variable Immunodeficiency and X-Linked Agammaglobulinaemia Patients. Endocr Metab Immune Disord Drug Targets. 2017;17:134-40.
125. Ruffner MA, Group UBW, Sullivan KE. Complications Associated with Underweight Primary Immunodeficiency Patients: Prevalence and Associations Within the USIDNET Registry. Journal of clinical immunology. 2018;38:283-93.
126. Yazdani R, Heydari A, Azizi G, Abolhassani H, Aghamohammadi A. Asthma and Allergic Diseases in a Selected Group of Patients With Common Variable Immunodeficiency. Journal of investigational allergology & clinical immunology. 2016;26:209-11.
127. Urm SH, Yun HD, Fenta YA, Yoo KH, Abraham RS, Hagan J, Juhn YJ. Asthma and risk of selective IgA deficiency or common variable immunodeficiency: a population-based case-control study. Mayo Clin Proc. 2013;88:813-21.
128. Agondi RC, Barros MT, Rizzo LV, Kalil J, Giavina-Bianchi P. Allergic asthma in patients with common variable immunodeficiency. Allergy. 2010;65:510-5.
129. Nguyen JT, Green A, Wilson MR, DeRisi JL, Gundling K. Neurologic Complications of Common Variable Immunodeficiency. Journal of clinical immunology. 2016;36:793-800.

doi: 10.18176/jiaci.0388

130. Kurmann R, Weisstanner C, Kardas P, Hirsch HH, Wiest R, Lammle B, Furrer H, Du Pasquier R, Bassetti CL, Sturzenegger M, Krestel H. Progressive multifocal leukoencephalopathy in common variable immunodeficiency: mitigated course under mirtazapine and mefloquine. J Neurovirol. 2015;21:694-701.
131. Snyder MD, Storch GA, Clifford DB. Atypical PML leading to a diagnosis of common variable immunodeficiency. Neurology. 2005;64:1661.
132. Jabbari E, Marshall CR, Longhurst H, Sylvester R. Longitudinally extensive transverse myelitis: a rare association with common variable immunodeficiency. Pract Neurol. 2015;15:49-52.
133. Danieli MG, Pettinari L, Marinangeli L, Logullo F. Recurrent myelitis in common variable immunodeficiency successfully managed with high-dose subcutaneous immunoglobulin. BMJ Case Rep. 2012;2012.
134. Megias MC, Matei AM, Gonzalez Albarran O, Perez Lopez G. Partial central diabetes insipidus in patient with common variable immunodeficiency. BMJ Case Rep. 2012;2012.
135. Tovo PA, Lala R, Martino S, Pastorelli G, De Sanctis C. Isolated adrenocorticotropic hormone deficiency associated with common variable immunodeficiency. Eur J Pediatr. 1991;150:400-2.
136. Aslam A, Misbah SA, Talbot K, Chapel H. Vitamin E deficiency induced neurological disease in common variable immunodeficiency: two cases and a review of the literature of vitamin E deficiency. Clinical immunology (Orlando, Fla). 2004;112:24-9.
137. Yousry TA, Strupp M, Bruning R. Common variable immunodeficiency leading to spinal subacute combined degeneration monitored by MRI. J Neurol Neurosurg Psychiatry. 1998;64:663-6.
138. Ward C, Lucas M, Piris J, Collier J, Chapel H. Abnormal liver function in common variable immunodeficiency disorders due to nodular regenerative hyperplasia. Clin Exp Immunol. 2008;153:331-7.
139. Cunningham-Rundles C, Bodian C. Common variable immunodeficiency: clinical and immunological features of 248 patients. Clinical immunology (Orlando, Fla). 1999;92:34-48.
140. Malamut G, Ziol M, Suarez F, Beaugrand M, Viallard JF, Lascaux AS, Verkarre V, Bechade D, Poynard T, Hermine O, Cellier C. Nodular regenerative hyperplasia: the main liver disease in patients with primary hypogammaglobulinemia and hepatic abnormalities. J Hepatol. 2008;48:74-82.
141. Ameratunga R, Brewerton M, Slade C, Jordan A, Gillis D, Steele R, Koopmans W, Woon ST. Comparison of diagnostic criteria for common variable immunodeficiency disorder. Frontiers in immunology. 2014;5:415.
142. Conley ME, Notarangelo LD, Etzioni A. Diagnostic criteria for primary immunodeficiencies. Representing PAGID (Pan-American Group for Immunodeficiency) and ESID (European Society for Immunodeficiencies). Clinical immunology (Orlando, Fla). 1999;93:190-7.
143. de Vries E, Driessen G. Educational paper: Primary immunodeficiencies in children: a diagnostic challenge. Eur J Pediatr. 2011;170:169-77.
144. Abolhassani H, Rezaei N, Mohammadinejad P, Mirminachi B, Hammarstrom L, Aghamohammadi A. Important differences in the diagnostic spectrum of primary immunodeficiency in adults versus children. Expert Rev Clin Immunol. 2015;11:289-302.
145. Azizi G, Abolhassani H, Habibi S, Rahamooz T, Mohammadi H, Jafarnezhad-Ansariha F, Mortazavi-Jahromi SS, Yazdani R, Aghamohammadi A. Two Faces of LRBA Deficiency in Siblings: Hypogammaglobulinemia and Normal Immunoglobulin Levels. Journal of investigational allergology & clinical immunology. 2018;28:48-50.
146. Lindegren ML, Kobrynski L, Rasmussen SA, Moore CA, Grosse SD, Vanderford ML, Spira TJ, McDougal JS, Vogt RF, Jr., Hannon WH, Kalman LV, Chen B, Mattson M, Baker TG, Khoury M. Applying public health strategies to primary immunodeficiency diseases: a potential approach to genetic disorders. MMWR Recommendations and reports : Morbidity and mortality weekly report Recommendations and reports. 2004;53:1-29.

doi: 10.18176/jiaci.0388

147. Reust CE. Evaluation of primary immunodeficiency disease in children. American family physician. 2013;87:773-8.
148. Tarzi MD, Grigoriadou S, Carr SB, Kuitert LM, Longhurst HJ. Clinical immunology review series: An approach to the management of pulmonary disease in primary antibody deficiency. Clin Exp Immunol. 2009;155:147-55.
149. Clutterbuck EA, Oh S, Hamaluba M, Westcar S, Beverley PC, Pollard AJ. Serotype-specific and age-dependent generation of pneumococcal polysaccharide-specific memory B-cell and antibody responses to immunization with a pneumococcal conjugate vaccine. Clinical and vaccine immunology : CVI. 2008;15:182-93.
150. Koch A, Melbye M, Sorensen P, Homoe P, Madsen HO, Molbak K, Hansen CH, Andersen LH, Hahn GW, Garred P. Acute respiratory tract infections and mannose-binding lectin insufficiency during early childhood. Jama. 2001;285:1316-21.
151. Stray-Pedersen A, Sorte HS, Samarakoon P, Gambin T, Chinn IK, Coban Akdemir ZH, Erichsen HC, Forbes LR, Gu S, Yuan B, Jhangiani SN, Muzny DM, Rodningen OK, Sheng Y, Nicholas SK, Noroski LM, Seeborg FO, Davis CM, Canter DL, Mace EM, Vece TJ, Allen CE, Abhyankar HA, Boone PM, Beck CR, Wiszniewski W, Fevang B, Aukrust P, Tjonnfjord GE, Gedde-Dahl T, Hjorth-Hansen H, Dybedal I, Nordoy I, Jorgensen SF, Abrahamsen TG, Overland T, Bechensteen AG, Skogen V, Osnes LTN, Kulseth MA, Prescott TE, Rustad CF, Heimdal KR, Belmont JW, Rider NL, Chinen J, Cao TN, Smith EA, Caldirola MS, Bezrodnik L, Lugo Reyes SO, Espinosa Rosales FJ, Guerrero-Cursaru ND, Pedroza LA, Poli CM, Franco JL, Trujillo Vargas CM, Aldave Becerra JC, Wright N, Issekutz TB, Issekutz AC, Abbott J, Caldwell JW, Bayer DK, Chan AY, Aiuti A, Cancrini C, Holmberg E, West C, Burstedt M, Karaca E, Yesil G, Artac H, Bayram Y, Atik MM, Eldomery MK, Ehlayel MS, Jolles S, Flato B, Bertuch AA, Hanson IC, Zhang VW, Wong LJ, Hu J, Walkiewicz M, Yang Y, Eng CM, Boerwinkle E, Gibbs RA, Shearer WT, Lyle R, Orange JS, Lupski JR. Primary immunodeficiency diseases: Genomic approaches delineate heterogeneous Mendelian disorders. J Allergy Clin Immunol. 2017;139:232-45.
152. Keller M, Glessner J, Resnick E, Perez E, Chapel H, Lucas M, Sullivan KE, Cunningham-Rundles C, Orange JS, Hakonarson H. Burden of copy number variation in common variable immunodeficiency. Clin Exp Immunol. 2014;177:269-71.
153. Orange JS, Glessner JT, Resnick E, Sullivan KE, Lucas M, Ferry B, Kim CE, Hou C, Wang F, Chiavacci R, Kugathasan S, Sleasman JW, Baldassano R, Perez EE, Chapel H, Cunningham-Rundles C, Hakonarson H. Genome-wide association identifies diverse causes of common variable immunodeficiency. J Allergy Clin Immunol. 2011;127:1360-7.e6.
154. Rehm HL, Bale SJ, Bayrak-Toydemir P, Berg JS, Brown KK, Deignan JL, Friez MJ, Funke BH, Hegde MR, Lyon E. ACMG clinical laboratory standards for next-generation sequencing. Genetics in medicine : official journal of the American College of Medical Genetics. 2013;15:733-47.
155. Casanova JL, Conley ME, Seligman SJ, Abel L, Notarangelo LD. Guidelines for genetic studies in single patients: lessons from primary immunodeficiencies. The Journal of experimental medicine. 2014;211:2137-49.
156. Mousallem T, Urban TJ, McSweeney KM, Kleinstein SE, Zhu M, Adeli M, Parrott RE, Roberts JL, Krueger B, Buckley RH, Goldstein DB. Clinical application of whole-genome sequencing in patients with primary immunodeficiency. J Allergy Clin Immunol. 2015;136:476-9.e6.
157. Hanitsch LG, Sotzny F, Volk HD, Scheibenbogen C, Wittke K. Serum Free Light Chains in CVID-a Marker for Differential Diagnosis. Journal of clinical immunology. 2018;38:163-5.
158. Salehzadeh M, Aghamohammadi A, Rezaei N. Evaluation of immunoglobulin levels and infection rate in patients with common variable immunodeficiency after immunoglobulin replacement therapy. Journal of microbiology, immunology, and infection = Wei mian yu gan ran za zhi. 2010;43:11-7.
159. Egawa M, Kanegane H, Imai K, Morio T, Miyasaka N. Intravenous immunoglobulin (IVIG) efficiency in women with common variable immunodeficiency (CVID) decreases significantly during

doi: 10.18176/jiaci.0388

pregnancy. The journal of maternal-fetal & neonatal medicine : the official journal of the European Association of Perinatal Medicine, the Federation of Asia and Oceania Perinatal Societies, the International Society of Perinatal Obstet. 2018;1-5.
160. Abolhassani H, Sagvand BT, Shokuhfar T, Mirminachi B, Rezaei N, Aghamohammadi A. A review on guidelines for management and treatment of common variable immunodeficiency. Expert Rev Clin Immunol. 2013;9:561-74; quiz 75.
161. Gardulf A, Abolhassani H, Gustafson R, Eriksson LE, Hammarstrom L. Predictive markers for humoral influenza vaccine response in patients with common variable immunodeficiency. J Allergy Clin Immunol. 2018.
162. Capistrano GG, Meneses GC, de Oliveira Neves FM, de Almeida Leitao R, Martins AMC, Liborio AB. Renal Evaluation in Common Variable Immunodeficiency. Journal of immunology research. 2018;2018:5841031.
163. Azizi G, Ziaee V, Tavakol M, Alinia T, Yazdai R, Mohammadi H, Abolhassani H, Aghamohammadi A. Approach to the Management of Autoimmunity in Primary Immunodeficiency. Scandinavian journal of immunology. 2017;85:13-29.
164. Castigli E, Wilson S, Garibyan L, Rachid R, Bonilla F, Schneider L, Morra M, Curran J, Geha R. Reexamining the role of TACI coding variants in common variable immunodeficiency and selective IgA deficiency. Nature genetics. 2007;39:430-1.
165. Wang HY, Ma CA, Zhao Y, Fan X, Zhou Q, Edmonds P, Uzel G, Oliveira JB, Orange J, Jain A. Antibody deficiency associated with an inherited autosomal dominant mutation in TWEAK. Proceedings of the National Academy of Sciences of the United States of America. 2013;110:5127-32.
166. van Montfrans JM, Hoepelman AI, Otto S, van Gijn M, van de Corput L, de Weger RA, Monaco-Shawver L, Banerjee PP, Sanders EA, Jol-van der Zijde CM, Betts MR, Orange JS, Bloem AC, Tesselaar K. CD27 deficiency is associated with combined immunodeficiency and persistent symptomatic EBV viremia. J Allergy Clin Immunol. 2012;129:787-93.e6.
167. Alkhairy OK, Perez-Becker R, Driessen GJ, Abolhassani H, van Montfrans J, Borte S, Choo S, Wang N, Tesselaar K, Fang M, Bienemann K, Boztug K, Daneva A, Mechinaud F, Wiesel T, Becker C, Duckers G, Siepermann K, van Zelm MC, Rezaei N, van der Burg M, Aghamohammadi A, Seidel MG, Niehues T, Hammarstrom L. Novel mutations in TNFRSF7/CD27: Clinical, immunologic, and genetic characterization of human CD27 deficiency. J Allergy Clin Immunol. 2015;136:703-12.e10.
168. Kanegane H, Agematsu K, Futatani T, Sira MM, Suga K, Sekiguchi T, van Zelm MC, Miyawaki T. Novel mutations in a Japanese patient with CD19 deficiency. Genes and immunity. 2007;8:663-70.
169. van Zelm MC, Reisli I, van der Burg M, Castano D, van Noesel CJ, van Tol MJ, Woellner C, Grimbacher B, Patino PJ, van Dongen JJ, Franco JL. An antibody-deficiency syndrome due to mutations in the CD19 gene. The New England journal of medicine. 2006;354:1901-12.
170. van Zelm MC, Smet J, Adams B, Mascart F, Schandene L, Janssen F, Ferster A, Kuo CC, Levy S, van Dongen JJ, van der Burg M. CD81 gene defect in humans disrupts CD19 complex formation and leads to antibody deficiency. The Journal of clinical investigation. 2010;120:1265-74.
171. Vences-Catalan F, Kuo CC, Sagi Y, Chen H, Kela-Madar N, van Zelm MC, van Dongen JJ, Levy S. A mutation in the human tetraspanin CD81 gene is expressed as a truncated protein but does not enable CD19 maturation and cell surface expression. Journal of clinical immunology. 2015;35:254-63.
172. van Zelm MC, Bartol SJ, Driessen GJ, Mascart F, Reisli I, Franco JL, Wolska-Kusnierz B, Kanegane H, Boon L, van Dongen JJ, van der Burg M. Human CD19 and CD40L deficiencies impair antibody selection and differentially affect somatic hypermutation. J Allergy Clin Immunol. 2014;134:135-44.
173. Kotlarz D, Zietara N, Uzel G, Weidemann T, Braun CJ, Diestelhorst J, Krawitz PM, Robinson PN, Hecht J, Puchalka J, Gertz EM, Schaffer AA, Lawrence MG, Kardava L, Pfeifer D, Baumann U, Pfister ED, Hanson EP, Schambach A, Jacobs R, Kreipe H, Moir S, Milner JD, Schwille P, Mundlos S, Klein C. Loss-of-

doi: 10.18176/jiaci.0388

function mutations in the IL-21 receptor gene cause a primary immunodeficiency syndrome. The Journal of experimental medicine. 2013;210:433-43.
174. Salzer E, Kansu A, Sic H, Majek P, Ikinciogullari A, Dogu FE, Prengemann NK, Santos-Valente E, Pickl WF, Bilic I, Ban SA, Kuloglu Z, Demir AM, Ensari A, Colinge J, Rizzi M, Eibel H, Boztug K. Early-onset inflammatory bowel disease and common variable immunodeficiency-like disease caused by IL-21 deficiency. J Allergy Clin Immunol. 2014;133:1651-9.e12.
175. Stepensky P, Keller B, Abuzaitoun O, Shaag A, Yaacov B, Unger S, Seidl M, Rizzi M, Weintraub M, Elpeleg O, Warnatz K. Extending the clinical and immunological phenotype of human interleukin-21 receptor deficiency. Haematologica. 2015;100:e72-6.
176. Ettinger R, Sims GP, Fairhurst AM, Robbins R, da Silva YS, Spolski R, Leonard WJ, Lipsky PE. IL-21 induces differentiation of human naive and memory B cells into antibody-secreting plasma cells. Journal of immunology (Baltimore, Md : 1950). 2005;175:7867-79.
177. Salzer U, Maul-Pavicic A, Cunningham-Rundles C, Urschel S, Belohradsky BH, Litzman J, Holm A, Franco JL, Plebani A, Hammarstrom L, Skrabl A, Schwinger W, Grimbacher B. ICOS deficiency in patients with common variable immunodeficiency. Clinical immunology (Orlando, Fla). 2004;113:234-40.
178. Kuijpers TW, Bende RJ, Baars PA, Grummels A, Derks IA, Dolman KM, Beaumont T, Tedder TF, van Noesel CJ, Eldering E, van Lier RA. CD20 deficiency in humans results in impaired T cell-independent antibody responses. The Journal of clinical investigation. 2010;120:214-22.
179. van der Heijden J, Geissler J, van Mirre E, van Deuren M, van der Meer JW, Salama A, van den Berg TK, Roos D, Kuijpers TW. A novel splice variant of FcgammaRIIa: a risk factor for anaphylaxis in patients with hypogammaglobulinemia. J Allergy Clin Immunol. 2013;131:1408-16.e5.
180. Flinsenberg TW, Janssen WJ, Herczenik E, Boross P, Nederend M, Jongeneel LH, Scholman RC, Boelens JJ, Maas C, van Gijn ME, van Montfrans JM, Leusen JH, Boes M. A novel FcgammaRIIa Q27W gene variant is associated with common variable immune deficiency through defective FcgammaRIIa downstream signaling. Clinical immunology (Orlando, Fla). 2014;155:108-17.
181. Yu JE, Zhang L, Radigan L, Sanchez-Ramon S, Cunningham-Rundles C. TLR-mediated B cell defects and IFN-alpha in common variable immunodeficiency. Journal of clinical immunology. 2012;32:50-60.
182. Kuehn HS, Ouyang W, Lo B, Deenick EK, Niemela JE, Avery DT, Schickel JN, Tran DQ, Stoddard J, Zhang Y, Frucht DM, Dumitriu B, Scheinberg P, Folio LR, Frein CA, Price S, Koh C, Heller T, Seroogy CM, Huttenlocher A, Rao VK, Su HC, Kleiner D, Notarangelo LD, Rampertaap Y, Olivier KN, McElwee J, Hughes J, Pittaluga S, Oliveira JB, Meffre E, Fleisher TA, Holland SM, Lenardo MJ, Tangye SG, Uzel G. Immune dysregulation in human subjects with heterozygous germline mutations in CTLA4. Science (New York, NY). 2014;345:1623-7.
183. Belot A, Kasher PR, Trotter EW, Foray AP, Debaud AL, Rice GI, Szynkiewicz M, Zabot MT, Rouvet I, Bhaskar SS, Daly SB, Dickerson JE, Mayer J, O'Sullivan J, Juillard L, Urquhart JE, Fawdar S, Marusiak AA, Stephenson N, Waszkowycz B, M WB, Biesecker LG, G CMB, Rene C, Eliaou JF, Fabien N, Ranchin B, Cochat P, Gaffney PM, Rozenberg F, Lebon P, Malcus C, Crow YJ, Brognard J, Bonnefoy N. Protein kinase cdelta deficiency causes mendelian systemic lupus erythematosus with B cell-defective apoptosis and hyperproliferation. Arthritis and rheumatism. 2013;65:2161-71.
184. Kuehn HS, Niemela JE, Rangel-Santos A, Zhang M, Pittaluga S, Stoddard JL, Hussey AA, Evbuomwan MO, Priel DA, Kuhns DB, Park CL, Fleisher TA, Uzel G, Oliveira JB. Loss-of-function of the protein kinase C delta (PKCdelta) causes a B-cell lymphoproliferative syndrome in humans. Blood. 2013;121:3117-25.
185. Salzer E, Santos-Valente E, Klaver S, Ban SA, Emminger W, Prengemann NK, Garncarz W, Mullauer L, Kain R, Boztug H, Heitger A, Arbeiter K, Eitelberger F, Seidel MG, Holter W, Pollak A, Pickl WF, Forster-Waldl E, Boztug K. B-cell deficiency and severe autoimmunity caused by deficiency of protein kinase C delta. Blood. 2013;121:3112-6.

doi: 10.18176/jiaci.0388

186. Gorjestani S, Yu M, Tang B, Zhang D, Wang D, Lin X. Phospholipase Cgamma2 (PLCgamma2) is key component in Dectin-2 signaling pathway, mediating anti-fungal innate immune responses. The Journal of biological chemistry. 2011;286:43651-9.
187. Ombrello MJ, Remmers EF, Sun G, Freeman AF, Datta S, Torabi-Parizi P, Subramanian N, Bunney TD, Baxendale RW, Martins MS, Romberg N, Komarow H, Aksentijevich I, Kim HS, Ho J, Cruse G, Jung MY, Gilfillan AM, Metcalfe DD, Nelson C, O'Brien M, Wisch L, Stone K, Douek DC, Gandhi C, Wanderer AA, Lee H, Nelson SF, Shianna KV, Cirulli ET, Goldstein DB, Long EO, Moir S, Meffre E, Holland SM, Kastner DL, Katan M, Hoffman HM, Milner JD. Cold urticaria, immunodeficiency, and autoimmunity related to PLCG2 deletions. The New England journal of medicine. 2012;366:330-8.
188. Elgizouli M, Lowe DM, Speckmann C, Schubert D, Hulsdunker J, Eskandarian Z, Dudek A, Schmitt-Graeff A, Wanders J, Jorgensen SF, Fevang B, Salzer U, Nieters A, Burns S, Grimbacher B. Activating PI3Kdelta mutations in a cohort of 669 patients with primary immunodeficiency. Clin Exp Immunol. 2016;183:221-9.
189. Lucas CL, Kuehn HS, Zhao F, Niemela JE, Deenick EK, Palendira U, Avery DT, Moens L, Cannons JL, Biancalana M, Stoddard J, Ouyang W, Frucht DM, Rao VK, Atkinson TP, Agharahimi A, Hussey AA, Folio LR, Olivier KN, Fleisher TA, Pittaluga S, Holland SM, Cohen JI, Oliveira JB, Tangye SG, Schwartzberg PL, Lenardo MJ, Uzel G. Dominant-activating germline mutations in the gene encoding the PI(3)K catalytic subunit p110delta result in T cell senescence and human immunodeficiency. Nature immunology. 2014;15:88-97.
190. Lucas CL, Zhang Y, Venida A, Wang Y, Hughes J, McElwee J, Butrick M, Matthews H, Price S, Biancalana M, Wang X, Richards M, Pozos T, Barlan I, Ozen A, Rao VK, Su HC, Lenardo MJ. Heterozygous splice mutation in PIK3R1 causes human immunodeficiency with lymphoproliferation due to dominant activation of PI3K. The Journal of experimental medicine. 2014;211:2537-47.
191. Deau MC, Heurtier L, Frange P, Suarez F, Bole-Feysot C, Nitschke P, Cavazzana M, Picard C, Durandy A, Fischer A, Kracker S. A human immunodeficiency caused by mutations in the PIK3R1 gene. The Journal of clinical investigation. 2014;124:3923-8.
192. Compeer EB, Janssen W, van Royen-Kerkhof A, van Gijn M, van Montfrans JM, Boes M. Dysfunctional BLK in common variable immunodeficiency perturbs B-cell proliferation and ability to elicit antigen-specific CD4+ T-cell help. Oncotarget. 2015;6:10759-71.
193. Fischer MB, Wolf HM, Hauber I, Eggenbauer H, Thon V, Sasgary M, Eibl MM. Activation via the antigen receptor is impaired in T cells, but not in B cells from patients with common variable immunodeficiency. European journal of immunology. 1996;26:231-7.
194. Li PL. Changes of intracellular IP3 with the expression of interleukin 2 receptor in human peripheral blood T lymphocytes. Journal of Tongji Medical University = Tong ji yi ke da xue xue bao. 1991;11:88-92.
195. Sawabe T, Horiuchi T, Nakamura M, Tsukamoto H, Nakahara K, Harashima SI, Tsuchiya T, Nakano S. Defect of lck in a patient with common variable immunodeficiency. International journal of molecular medicine. 2001;7:609-14.
196. Capitani N, Amedei A, Paccani SR, Matucci A, Vultaggio A, Del Prete G, Baldari CT, D'Elios MM. Impaired TH2 response in patients with Vav1-deficient common variable immunodeficiency with T-cell defects. J Allergy Clin Immunol. 2010;126:671-5.
197. Capitani N, Ariani F, Amedei A, Pezzicoli A, Matucci A, Vultaggio A, Troilo A, Renieri A, Baldari CT, MM DE. Vav1 haploinsufficiency in a common variable immunodeficiency patient with defective T-cell function. International journal of immunopathology and pharmacology. 2012;25:811-7.
198. Kurkchubasche AG, Panepinto JA, Tracy TF, Jr., Thurman GW, Ambruso DR. Clinical features of a human Rac2 mutation: a complex neutrophil dysfunction disease. The Journal of pediatrics. 2001;139:141-7.

doi: 10.18176/jiaci.0388

199. Ambruso DR, Knall C, Abell AN, Panepinto J, Kurkchubasche A, Thurman G, Gonzalez-Aller C, Hiester A, deBoer M, Harbeck RJ, Oyer R, Johnson GL, Roos D. Human neutrophil immunodeficiency syndrome is associated with an inhibitory Rac2 mutation. Proceedings of the National Academy of Sciences of the United States of America. 2000;97:4654-9.
200. Alkhairy OK, Rezaei N, Graham RR, Abolhassani H, Borte S, Hultenby K, Wu C, Aghamohammadi A, Williams DA, Behrens TW, Hammarstrom L, Pan-Hammarstrom Q. RAC2 loss-of-function mutation in 2 siblings with characteristics of common variable immunodeficiency. J Allergy Clin Immunol. 2015;135:1380-4 e1-5.
201. Boncristiano M, Majolini MB, D'Elios MM, Pacini S, Valensin S, Ulivieri C, Amedei A, Falini B, Del Prete G, Telford JL, Baldari CT. Defective recruitment and activation of ZAP-70 in common variable immunodeficiency patients with T cell defects. European journal of immunology. 2000;30:2632-8.
202. Lo B, Zhang K, Lu W, Zheng L, Zhang Q, Kanellopoulou C, Zhang Y, Liu Z, Fritz JM, Marsh R, Husami A, Kissell D, Nortman S, Chaturvedi V, Haines H, Young LR, Mo J, Filipovich AH, Bleesing JJ, Mustillo P, Stephens M, Rueda CM, Chougnet CA, Hoebe K, McElwee J, Hughes JD, Karakoc-Aydiner E, Matthews HF, Price S, Su HC, Rao VK, Lenardo MJ, Jordan MB. AUTOIMMUNE DISEASE. Patients with LRBA deficiency show CTLA4 loss and immune dysregulation responsive to abatacept therapy. Science (New York, NY). 2015;349:436-40.
203. Lopez-Herrera G, Tampella G, Pan-Hammarstrom Q, Herholz P, Trujillo-Vargas CM, Phadwal K, Simon AK, Moutschen M, Etzioni A, Mory A, Srugo I, Melamed D, Hultenby K, Liu C, Baronio M, Vitali M, Philippet P, Dideberg V, Aghamohammadi A, Rezaei N, Enright V, Du L, Salzer U, Eibel H, Pfeifer D, Veelken H, Stauss H, Lougaris V, Plebani A, Gertz EM, Schaffer AA, Hammarstrom L, Grimbacher B. Deleterious mutations in LRBA are associated with a syndrome of immune deficiency and autoimmunity. American journal of human genetics. 2012;90:986-1001.
204. Gamez-Diaz L, August D, Stepensky P, Revel-Vilk S, Seidel MG, Noriko M, Morio T, Worth AJJ, Blessing J, Van de Veerdonk F, Feuchtinger T, Kanariou M, Schmitt-Graeff A, Jung S, Seneviratne S, Burns S, Belohradsky BH, Rezaei N, Bakhtiar S, Speckmann C, Jordan M, Grimbacher B. The extended phenotype of LPS-responsive beige-like anchor protein (LRBA) deficiency. J Allergy Clin Immunol. 2016;137:223-30.
205. Visentini M, Marrapodi R, Conti V, Mitrevski M, Camponeschi A, Lazzeri C, Carbonari M, Catizone A, Quinti I, Fiorilli M. Dysregulated extracellular signal-regulated kinase signaling associated with impaired B-cell receptor endocytosis in patients with common variable immunodeficiency. J Allergy Clin Immunol. 2014;134:401-10.
206. Stepensky P, Keller B, Buchta M, Kienzler AK, Elpeleg O, Somech R, Cohen S, Shachar I, Miosge LA, Schlesier M, Fuchs I, Enders A, Eibel H, Grimbacher B, Warnatz K. Deficiency of caspase recruitment domain family, member 11 (CARD11), causes profound combined immunodeficiency in human subjects. J Allergy Clin Immunol. 2013;131:477-85.e1.
207. Tampella G, Baronio M, Vitali M, Soresina A, Badolato R, Giliani S, Plebani A, Lougaris V. Evaluation of CARMA1/CARD11 and Bob1 as candidate genes in common variable immunodeficiency. Journal of investigational allergology & clinical immunology. 2011;21:348-53.
208. Lindner JM, Wong CS, Moller A, Nielsen PJ. A C-terminal acidic domain regulates degradation of the transcriptional coactivator Bob1. Molecular and cellular biology. 2013;33:4628-40.
209. Plebani A, Lougaris V, Soresina A, Meini A, Zunino F, Losi CG, Gatta R, Cattaneo G, Nespoli L, Marinoni M, Capolunghi F, Vivarelli M, Quinti I, Carsetti R. A novel immunodeficiency characterized by the exclusive presence of transitional B cells unresponsive to CpG. Immunology. 2007;121:183-8.
210. Chen K, Coonrod EM, Kumanovics A, Franks ZF, Durtschi JD, Margraf RL, Wu W, Heikal NM, Augustine NH, Ridge PG, Hill HR, Jorde LB, Weyrich AS, Zimmerman GA, Gundlapalli AV, Bohnsack JF, Voelkerding KV. Germline mutations in NFKB2 implicate the noncanonical NF-kappaB pathway in the

doi: 10.18176/jiaci.0388

pathogenesis of common variable immunodeficiency. American journal of human genetics. 2013;93:812-24.
211. Shi C, Wang F, Tong A, Zhang XQ, Song HM, Liu ZY, Lyu W, Liu YH, Xia WB. NFKB2 mutation in common variable immunodeficiency and isolated adrenocorticotropic hormone deficiency: A case report and review of literature. Medicine. 2016;95:e5081.
212. Liu Y, Hanson S, Gurugama P, Jones A, Clark B, Ibrahim MA. Novel NFKB2 mutation in early-onset CVID. Journal of clinical immunology. 2014;34:686-90.
213. Kuehn HS, Boisson B, Cunningham-Rundles C, Reichenbach J, Stray-Pedersen A, Gelfand EW, Maffucci P, Pierce KR, Abbott JK, Voelkerding KV, South ST, Augustine NH, Bush JS, Dolen WK, Wray BB, Itan Y, Cobat A, Sorte HS, Ganesan S, Prader S, Martins TB, Lawrence MG, Orange JS, Calvo KR, Niemela JE, Casanova JL, Fleisher TA, Hill HR, Kumanovics A, Conley ME, Rosenzweig SD. Loss of B Cells in Patients with Heterozygous Mutations in IKAROS. The New England journal of medicine. 2016;374:1032-43.
214. Kobbe R, Kolster M, Fuchs S, Schulze-Sturm U, Jenderny J, Kochhan L, Staab J, Tolosa E, Grimbacher B, Meyer T. Common variable immunodeficiency, impaired neurological development and reduced numbers of T regulatory cells in a 10-year-old boy with a STAT1 gain-of-function mutation. Gene. 2016;586:234-8.
215. Keller MD, Pandey R, Li D, Glessner J, Tian L, Henrickson SE, Chinn IK, Monaco-Shawver L, Heimall J, Hou C, Otieno FG, Jyonouchi S, Calabrese L, van Montfrans J, Orange JS, Hakonarson H. Mutation in IRF2BP2 is responsible for a familial form of common variable immunodeficiency disorder. J Allergy Clin Immunol. 2016;138:544-50.e4.
216. Abolhassani H, Edwards ES, Ikinciogullari A, Jing H, Borte S, Buggert M, Du L, Matsuda-Lennikov M, Romano R, Caridha R, Bade S, Zhang Y, Frederiksen J, Fang M, Bal SK, Haskologlu S, Dogu F, Tacyildiz N, Matthews HF, McElwee JJ, Gostick E, Price DA, Palendira U, Aghamohammadi A, Boisson B, Rezaei N, Karlsson AC, Lenardo MJ, Casanova JL, Hammarstrom L, Tangye SG, Su HC, Pan-Hammarstrom Q. Combined immunodeficiency and Epstein-Barr virus-induced B cell malignancy in humans with inherited CD70 deficiency. The Journal of experimental medicine. 2017;214:91-106.
217. Schubert D, Klein MC, Hassdenteufel S, Caballero-Oteyza A, Yang L, Proietti M, Bulashevska A, Kemming J, Kuhn J, Winzer S, Rusch S, Fliegauf M, Schaffer AA, Pfeffer S, Geiger R, Cavalie A, Cao H, Yang F, Li Y, Rizzi M, Eibel H, Kobbe R, Marks AL, Peppers BP, Hostoffer RW, Puck JM, Zimmermann R, Grimbacher B. Plasma cell deficiency in human subjects with heterozygous mutations in Sec61 translocon alpha 1 subunit (SEC61A1). J Allergy Clin Immunol. 2018;141:1427-38.
218. Jansen EJ, Timal S, Ryan M, Ashikov A, van Scherpenzeel M, Graham LA, Mandel H, Hoischen A, Iancu TC, Raymond K, Steenbergen G, Gilissen C, Huijben K, van Bakel NH, Maeda Y, Rodenburg RJ, Adamowicz M, Crushell E, Koenen H, Adams D, Vodopiutz J, Greber-Platzer S, Muller T, Dueckers G, Morava E, Sykut-Cegielska J, Martens GJ, Wevers RA, Niehues T, Huynen MA, Veltman JA, Stevens TH, Lefeber DJ. ATP6AP1 deficiency causes an immunodeficiency with hepatopathy, cognitive impairment and abnormal protein glycosylation. Nature communications. 2016;7:11600.
219. Rider NL, Boisson B, Jyonouchi S, Hanson EP, Rosenzweig SD, Cassanova JL, Orange JS. Novel TTC37 Mutations in a Patient with Immunodeficiency without Diarrhea: Extending the Phenotype of Trichohepatoenteric Syndrome. Frontiers in pediatrics. 2015;3:2.
220. Chakraborty PK, Schmitz-Abe K, Kennedy EK, Mamady H, Naas T, Durie D, Campagna DR, Lau A, Sendamarai AK, Wiseman DH, May A, Jolles S, Connor P, Powell C, Heeney MM, Giardina PJ, Klaassen RJ, Kannengiesser C, Thuret I, Thompson AA, Marques L, Hughes S, Bonney DK, Bottomley SS, Wynn RF, Laxer RM, Minniti CP, Moppett J, Bordon V, Geraghty M, Joyce PB, Markianos K, Rudner AD, Holcik M, Fleming MD. Mutations in TRNT1 cause congenital sideroblastic anemia with immunodeficiency, fevers, and developmental delay (SIFD). Blood. 2014;124:2867-71.

doi: 10.18176/jiaci.0388

221. Tsujita Y, Mitsui-Sekinaka K, Imai K, Yeh TW, Mitsuiki N, Asano T, Ohnishi H, Kato Z, Sekinaka Y, Zaha K, Kato T, Okano T, Takashima T, Kobayashi K, Kimura M, Kunitsu T, Maruo Y, Kanegane H, Takagi M, Yoshida K, Okuno Y, Muramatsu H, Shiraishi Y, Chiba K, Tanaka H, Miyano S, Kojima S, Ogawa S, Ohara O, Okada S, Kobayashi M, Morio T, Nonoyama S. Phosphatase and tensin homolog (PTEN) mutation can cause activated phosphatidylinositol 3-kinase delta syndrome-like immunodeficiency. J Allergy Clin Immunol. 2016;138:1672-80.e10.
222. Taubenheim N, von Hornung M, Durandy A, Warnatz K, Corcoran L, Peter HH, Eibel H. Defined blocks in terminal plasma cell differentiation of common variable immunodeficiency patients. Journal of immunology (Baltimore, Md : 1950). 2005;175:5498-503.
223. Rezaei N, Aghamohammadi A, Kardar GA, Nourizadeh M, Pourpak Z. T- helper 1 and 2 cytokine assay in patients with common variable immunodeficiency. Journal of investigational allergology & clinical immunology. 2008;18:449-53.
224. Katial RK, Lieberman MM, Muehlbauer SL, Lust JA, Hamilos DL. Gamma delta T lymphocytosis associated with common variable immunodeficiency. Journal of clinical immunology. 1997;17:34-42.
225. Viallard JF, Bloch-Michel C, Caubet O, Parrens M, Texier-Maugein J, Neau-Cransac M, Taupin JL, Moreau JF, Pellegrin JL. Gammadelta T lymphocytosis associated with granulomatous disease in a patient with common variable immunodeficiency. Clin Infect Dis. 2002;35:e134-7.
226. Viallard JF, Camou F, Andre M, Liferman F, Moreau JF, Pellegrin JL, Blanco P. Altered dendritic cell distribution in patients with common variable immunodeficiency. Arthritis research & therapy. 2005;7:R1052-5.
227. Martinez-Pomar N, Raga S, Ferrer J, Pons J, Munoz-Saa I, Julia MR, de Gracia J, Matamoros N. Elevated serum interleukin (IL)-12p40 levels in common variable immunodeficiency disease and decreased peripheral blood dendritic cells: analysis of IL-12p40 and interferon-gamma gene. Clin Exp Immunol. 2006;144:233-8.
228. Cols M, Rahman A, Maglione PJ, Garcia-Carmona Y, Simchoni N, Ko HM, Radigan L, Cerutti A, Blankenship D, Pascual V, Cunningham-Rundles C. Expansion of inflammatory innate lymphoid cells in patients with common variable immune deficiency. J Allergy Clin Immunol. 2016;137:1206-15.e6.

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Table1. Surface molecular defects in CVID patients

Name of Genes	Functions	Ref
TACI (encoded by TNFRSF13B)	**Function:** Regulation of BCR, TLR7, and TLR9 function **Effect of deficiency:** B cell activation defect and also autoimmunity manifestation	[18, 20, 164]
BAFF-R(encoded by TNFRSF13C)	**Function:** Regulation of B cell survival and maturation **Effect of deficiency:** Low peripheral B-cell numbers, Increased transitional B cells, decreased antibody responses to polysaccharidevaccine	[43]
TWEAK(encoded by TNFRSF12)	**Function:** Promotion of endothelial cells proliferation and polarization of immune responses to Th1 adaptive responses **Effect of deficiency:** Inhibition of B-cell survival and proliferation, Inhibition of Ig class switching by down regulation of the noncanonical BAFF-induced NF-κB pathway	[165]
CD27 (encoded by TNFRSF7)	**Function:** Participation in T, B and NK-cell function **Effect of deficiency:** Hypogammaglobulinemia, abnormal T-cell dependent B-cell response, disturbed T-cell function, absent memory B cell	[166, 167]
CD19 complex(CD19, CD81 and CD21)	**Function**: Attenuation of B cell activation threshold and thus signaling enhancement as a result of co-ligation of this complex by B cell receptor. **Effect of deficiency:** Impaired BCR/co-receptor complex signaling, defective somatic hypermutation and CSR, reduced memory B cells and plasma cells, are seen in both CD19 and CD81 deficient patients. Hypogammaglobulinemia, reduced number of memory B cells and increased naïve mature B cells have been observed in CD21 deficient patients.	[168-172]
IL21R and its ligand (IL21)	**Function:** IL21-IL21R interaction is required for germinal center formation, proliferation and class switch recombination of B cells, plasma cell differentiation and eventually immunoglobulin production. **Effect of deficiency:** defects in class switch recombination, variable dysfunctions of NK cell cytotoxicity, decreased T cell proliferation, reduced numbers of circulating, marginal zone-like and class-switched memory B cells, increased number of transitional ones, increased IgE levels and reduced IgG levels.	[173-176]
ICOS	**Function:** Regulation of terminal B cell differentiation in germinal centers, T cell tolerance and also effector T cell responses. **Effect of deficiency:** Severe reduction in B lymphocyte counts, low levels of serum concentrations of IgM and switched Ig isotype, lack of the expression of maturation and memory marker CD27 on B cells	[177]
CD20 (MS4A1)	**Function:** Regulation of Ca2+ transport across the plasma membrane. **Effect of deficiency:** Severe reduction in switched memory B cells, decreased IgG level with relatively increased IgM and weak responses against polysaccharides after vaccination, reduction in the frequency of somatic hypermutation in IgG heavy chain	[178]
FCγRIIa	**Function:** Recognition of FC region of immunoglobulin G **Effect of deficiency:** Increased sensitivity of neutrophils to immune complexes, anaphylactoid reactions to immunoglobulin infusions, suppress signaling cascade in B cells due to MAPK phosphorylation	[179, 180]
CTLA-4	**Function:** Suppression of immune responses by negative signaling and therefore preventing excessive T cell activation **Effect of deficiency:** Impaired function of Treg cells, reduced circulating B cells, increased autoreactive CD21low	[181, 182]

BCR: B cell receptor, TLR: Toll-like receptors, BAFF: B-cell activating factor, Th: T helper cells, CSR: class switch recombination, NF-κB *: nuclear factor kappa-light-chain-enhancer of activated B cells.*

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Table2. Cytosolic defects in CVID patients

Name of Genes	Functions	Ref
PKCδ	**Function:** Involved in BCR mediated signaling and is participated in the regulation of cellular process including proliferation, differentiation, apoptosis and tolerance **Effect of deficiency:** Decrease of CD19 B cells, low numbers of memory B cells, as well as increased numbers of $CD21^{low}$ B cells	[183-185]
PLCγ2	**Function:** Participation in B cell receptor signaling **Effect of deficiency:** Defective calcium flux and phosphorylation of ERK in response to IgM crosslinking, abnormal class switch recombination and receptor editing and also antibody deficiency	[186, 187]
PI3K (PI3KR1, PI3LCD)	**Function:** B and T cell homoeostasis **Effect of deficiency:** Expanded CD8 T cells, agammaglobulinemia, increased the frequency of transitional B cells, decreased numbers of naive CD4 and CD8 T cells and increased numbers of CD8 effector/memory T cell, normal or often increased serum IgM kevels, increased T cell activation-induced cell death	[188-191]
BLK	**Function:** Member of the Src kinase family which is involved in BCR signaling **Effect of deficiency:** Diminished B-cell proliferation and T-cell help and subsequently reduced numbers of class-switched memory B-cells and defective production of high affinity antibody	[192]
IP3	**Function:** Induction of calcium mobilization to the cytosol, resulting in elevation of the intracellular $Ca2^{+}$ that is necessary for the induction of the IL-2 gene **Effect of deficiency:** Defect in TCR signaling	[193, 194]
LCK	**Function:** A tyrosine kinase associated with the cytoplasmic tails of CD4 and CD8 in T-cells and is involved in the maturation, activation and differentiation of T cells **Effect of deficiency:** Normal T cell number, reduced T regulatory cells, impaired TCR signaling and restricted T cell repertoire	[195]
Vav1	**Function:** Required for T cell activation and T helper polarization to Th2 subsets **Effect of deficiency:** T cell dysfunction	[196, 197]
Rac2	**Function:** A member of the Rho family of GTPase that are crucial regulators of cell signaling and actin cytoskeleton **Effect of deficiency:** Reduced chemotaxis activity, reduced numbers of neutrophil granules as well as morphological changes of the secondary granules, defects in B and T cells development	[198-200]
ZAP70	**Function:** A member of the Syk family of tyrosine kinases that play an important role in T cell activation **Effect of deficiency**: Impaired T cell function due to defective recruitment and activation of ZAP70	[201]
LRBA	**Function:** A cytosolic protein participate in multiple cellular functions such as vesicular trafficking, signal transduction, cytoskeleton assembly, transcriptional regulation, autophagy and apoptosis **Effect of deficiency:** Hypogammaglobulinemia and reduced switched memory B cells as well as different clinical manifestation such as autoimmunity, enteropathy, and recurrent respiratory infections	[202-204]
ERK	**Function:** A serine/threonine kinase that phosphorylates various substrates and plays important roles in cell proliferation, differentiation, migration and survival **Effect of deficiency:** Dysregulation of BCR induced ERK activation in naïve and IgM memory B cells, blocking of BCR endocytosis and B cell dysfunction especially in CVID patients with $CD21^{low}$ phenotype	[205]
CARMA1/CARD11	**Function:** T and B cell activation through NF-kB activation after TCR and BCR cross-linking **Effect of deficiency:** Impaired B cell differentiation and T cell proliferation, reduced number of T regulatory cells and increased number of	[206, 207]

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	transitional B cells		
Bob1	**Function:** A B-cell–specific transcriptional co-activator that stimulates transcription in selected immunoglobulin genes **Effect of deficiency:** Decreased B cell production and activation, impaired germinal center formation and reduced class switched immunoglobulins		[207, 208]
TLRs	***TLR9***	**Function:** Recognition of DNA-containing CpG motifs derived from microbes and play key roles in the activation of immune responses **Effect of deficiency:** Normal number of B cells but decreased circulating memory and switched memory $CD27^{+}$B cells, decreased plasma cells and increased transitional B cells	[73, 181, 209]
	TLR7	**Function:** : Recognition of single-stranded RNA derived from microbes **Effect of deficiency:** Defective B cells proliferation, lack cytokine production, impaired IgG and IgA production in both naïve and memory B cells. These defects are also seen in pDCs as it is demonstrated that these cells fail to produce IFN-α in response to TLR ligands	

BCR: B cell receptor, TCR: T cell receptor, GTPase: guanosine triphosphateas, NF-κB*: nuclear factor kappa-light-chain-enhancer of activated B cells,* pDCs: *Plasmacytoid dendritic cells, TLR: Toll-like receptors.*

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Table 3. Nucleus defects in CVID patients

Name of Genes	Functions	Ref
NFKB (NFKB1, NFKB2)	**Function:** NFKB signaling play important roles in B cell maturation, differentiation, survival, class switching and tolerance to self-antigens **Effect of deficiency:** Defective development or maintenance of Tfh cells, Impaired T cell and NK cell functions, reduced switched memory B cell counts, (pan) hypogammaglobulinemia	[210-212]
IKZF1	**Function:** A member of a family of hematopoietic zinc-finger transcription factors that play key roles in B cell lymphopoiesis and function. **Effect of deficiency:** Panhypogammaglobulinaemia, low B cell number with a progressive loss of serum immunoglobulins and B cells	[213]
STAT1	**Function:** A member of the transcription protein family important in many biological processes. **Effect of deficiency:** Hypogammaglobulinemia, reduced switched memory and plasma cells, increased proportion of naïve, $CD21^{low}$ and transitional B cells as well as reduced numbers of IL-17-producing $CD4^+$ T cells and T regulatory cells	[214]
IRF2BP2 (Interferon regulatory factor 2 binding protein 2)	**Function:** A negative regulator of the NFAT transcription factor, play a role in the differentiation and/or survival of memory B cells and plasmablasts **Effect of deficiency:** Relative decrease in switched memory B-cells, undetectable IgG2, absent IgA and low IgM, decreased the formation of B-cell plasmablasts	[215]
NEIL1	**Function:** DNA glycosylases that participate in base excision repair and B cells development and function **Effect of deficiency:** Increased naïve memory B-cells (IgD^+CD27^-), reduced count of marginal zone B-cells (IgD^+CD27^+) and an almost complete absence of class switched memory B-cells and low level of immunoglobulins	[216]
SEC61A1	**Function:** The major subunit of the Sec61 complex, which is the 57 main polypeptide-conducting channels in the endoplasmic reticulum membrane which is strongly induced during plasma cell differentiation. **Effect of deficiency:** Impaired plasma cell homeostasis without interfering with B cell development, activation, and memory formation	[217]
CD70	**Function:** Participation in T cell expansion and survival, germinal center formation, B cell activation and antibody production, and NK cell function **Effect of deficiency:** Increased susceptibility to EBV-induced disease as well as impairments in T and B cell differentiation, hypogammaglobulinemia, poor Ab responses to vaccinations, and/or a reduced percentage of switched memory B cells	[216]
ATP6AP1	**Function:** This gene encodes the accessory protein Ac45 of the V-ATPase **Effect of deficiency:** Hypogammaglobulinemia, problem in B-cell differentiation	[218]
TTC37	**Function:** This gene encodes members of the human Ski complex, which functions in exosomal RNA degradation **Effect of deficiency:** Specific antibody deficiency with impairment of humoral memory	[219]
TRNT1	**Function:** A template-independent RNA polymerase essential for maturation of both nuclear and mitochondrial transfer RNAs **Effect of deficiency:** B-cell immunodeficiency	[220]
PTEN	**Function:** Downregulation of AKT signaling in the mTOR pathway which is critical for cell survival, proliferation, growth, and metabolism **Effect of deficiency:** Hypogammaglobulinemia, reduced numbers of memory B cells and class-switched memory ($CD27^+IgM^-IgD^-$) B cells	[221]

NF-κB: nuclear factor kappa-light-chain-enhancer of activated B cells, Tfh: T follicular helper cells, NFAT: nuclear factor of activated T cells

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Table 4. Abnormalities and Functions of different immune cells in CVID

Cell Type	Subsets	Increased/Decreased	Ref
B cell	Transitional B cells	Increased	[42]
	$CD21^{low}$ B cells	Increased	[43]
	IgM memory B cells ($CD19^{+}/CD27^{+}$),	Decreased	[34]
	Class switched memory B cells ($CD19^{+}/CD27^{+}/IgD^{-}/IgM^{-}$)	Decreased	[39]
	Plasma cells	Decreased	[40, 222]
T cell	Naïve $CD4^{+}$ T cells	Decreased	[46, 48]
	Effector memory $CD4^{+}$ T cells	Increased (in all 3 groups Ia/Ib/II)	[46]
	Central memory $CD4^{+}$ T cells	Increased (in all 3 groups Ia/Ib/II)	[46]
	Activated $CD4^{+}$ T cells	Increased	[46]
	Th1/ Th2	Trend towards Th1 or Th2	[50-52, 223]
	Th17 cells	Decreased	[53]
	Follicular T helpers ($CD4^{+}/CXCR5^{+}$) cells	Increased/ Decreased	[55, 56, 58]
	T regulatory cells	No difference between the patients and healthy control/ Decreased	[48, 60, 61, 67]
	Naïve $CD8^{+}$ T cells	Decreased	[48]
	Effector memory $CD8^{+}$ T cell	Increased (in all 3 groups Ia/Ib/II)	[46, 48]
	Central memory $CD8^{+}$ T cell	Increased (in group I)	[46]
	Activated $CD8^{+}$ T cells	Increased	[66, 67]
	$\gamma\delta^{+}$ T cells	Increased	[70, 224, 225]
Dendritic Cells	DCs cells	Decreased	[74, 226, 227]
Monocytes/Macrophages	IL-12^{+} monocytes	Increased	[77]
ILC	IL-$17^{+}CD127^{+}Thy1^{+}$ Lin^{-} cells	Decreased	[54]
	$Lin^{-}CD127^{+}$ cells producing IFN-ɣ, IL-17A and IL-22	Increased	[228]
	$CD3^{-}CD16^{+}CD56^{+}CD28^{+}$ NK cells	Increased	[83]

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	$CD3^{-}CD16^{+}CD56^{+}CD28^{-}$ NK cells	Decreased	[83]
NKT	NKT cells	No difference between the patients and healthy control.	[85]
iNKT	iNKT cells	Decreased	[86]

NKT: Natural killer T, iNKT: Invariant natural killer T

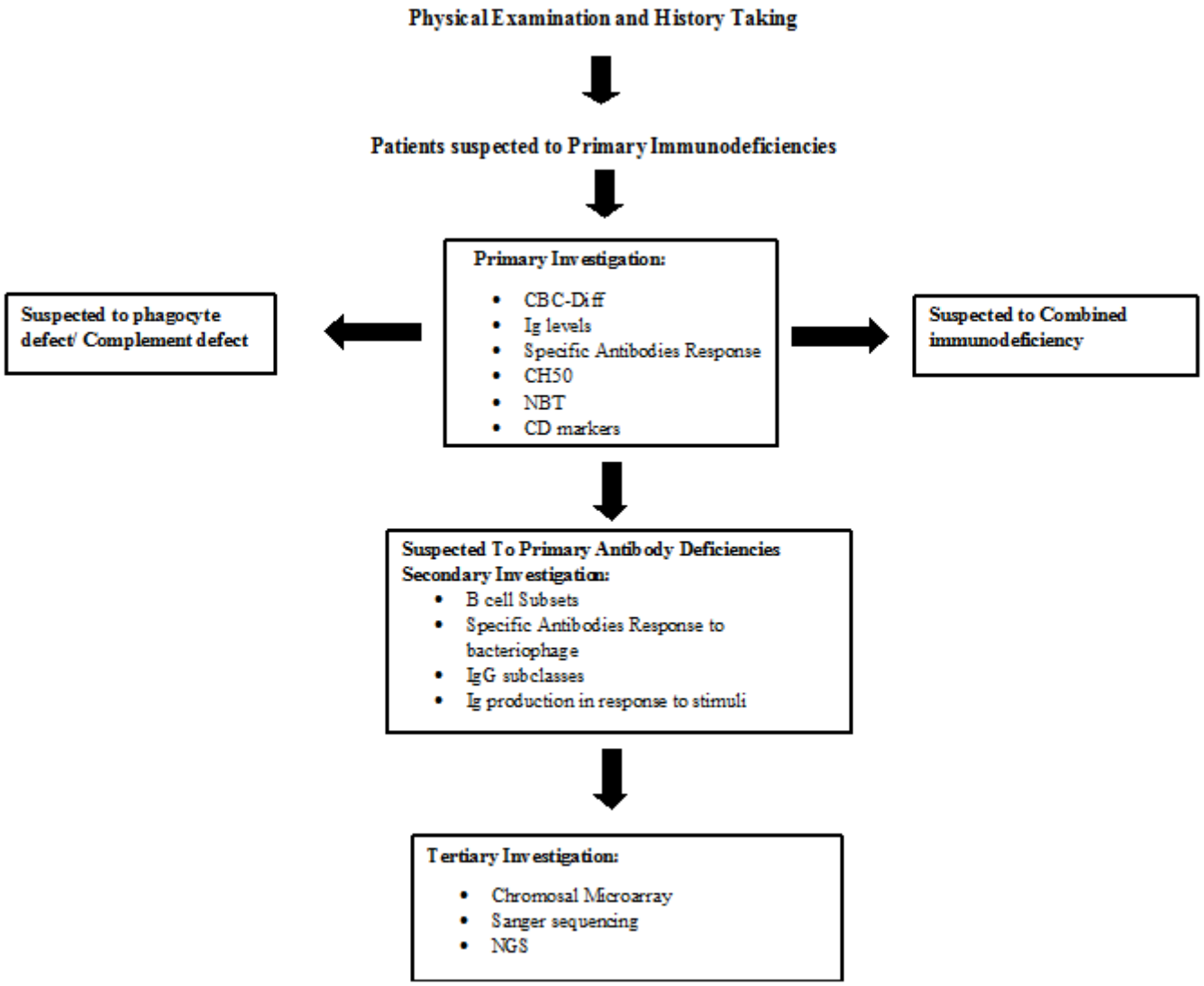

Figure 1. **General approach for the diagnosis of CVID**. After physical examination and history-taking, the physician should evaluate patients suspected to primary immunodeficiencies in three steps of initial, secondary and tertiary evaluations for diagnosis of CVID patients.

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