Invited Review

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Pulmonary Complications of Monogenic Patients with Common Variable Immunodeficiency: COVID-19 Perspectives

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Abstract

Pulmonary complications are one the main causes of morbidity and mortality in patients with common variable immunodeficiency (CVID). Although CVID pathogenesis is not completely understood, several genes have been identified to mainly regulate the process of terminal B-cell differentiation, antibody isotype maturation and long-life memory/plasma cell generation. The link between underlying genetic defects and the prognosis of developing different clinical complications like different pulmonary manifestations is still elusive. We provide an overview of recent advancements in the monogenic form of CVID which lead to dysregulation of B-cells at different levels of cytokine stimulations, intracellular signaling, transcription-factor activation, gene transcription and epigenetic controls and predispose patients to different pulmonary complications. The susceptibility to Coronavirus disease 2019 pulmonary complications was discussed in these patients. Monogenic forms of CVID have a distinct pattern in different infectious and non-infectious pulmonary manifestations including autoimmunity, atopy, lymphoproliferation, and cancer.

Keywords: Primary immunodeficiency, inborn errors of immunity, common variable immunodeficiency, genetic, respiratory complications

Article Highlights

- The majority of patients with monogenic common variable immunodeficiency (CVID) defects manifest diverse pulmonary complications.
- Specific types of monogenic CVID defects can present non-infectious pulmonary manifestations including interstitial lung disease, atopy, lymphoproliferation, and malignancy.

Introduction

Terminal B-cell immune system defects cause common variable immunodeficiency (CVID). CVID patients are more susceptible to experiencing recurrent infections [mainly due to lack of production of immunoglobulins (Igs)] and non-infectious complications (mainly due to humoral immune dysregulation) (1-3). As the most common symptomatic entity of inborn errors of immunity, CVID cases are often affected by complications in the respiratory tract system. Of note, retrospective studies also indicated that pulmonary features were the main initial manifestation in the majority of documented patients (4). Pulmonary complications in CVID patients increase significantly the risk of morbidity and mortality as the majority of deceased individuals in different age groups are due to respiratory failure (5,6). Therefore, one of the main optimal goals in the management of these patients is to avoid respiratory

complications through early detection and appropriate treatment (7,8).

Due to the wide spectrum of CVID pulmonary diseases (3), clinical immunologists and pulmonologists divided them into upper respiratory complications (e.g. sinusitis, otitis media, chronic cough, tonsillitis, pharyngitis, laryngitis, epiglottitis, infectious mononucleosis, allergic rhinitis) and lower respiratory complications (e.g. pneumonia, bronchitis, empyema, purulent pleuritis, bronchiectasis, interstitial lung diseases, organizing pneumonia, pulmonary adenopathies, malignancies, hyperreactive airway diseases, and adverse reactions to treatment) (9,10).

Expectedly, the majority of the abovementioned CVID pulmonary complications are characterized by recurrent infections. The isolated pathogens are typically encapsulated bacteria: *Streptococcus pneumonia, Haemophilus influenzae*, and *Staphylococcus* species. Due to the fact that vaccine-preventable infections (e.g., *Bordetella pertussis*) are also associated with antibody deficiencies, these pathogens could also be the etiological agents of pulmonary infections in CVID patients (3). Of note, exacerbations in the early phase of the disease are usually due to *H. influenzae* and *S. pneumoniae*, while in the later stages and when CVID patients develop a chronic lung sequel, *Pseudomonas* spp. and *Staphylococcus aureus* become the main identified pathogens (9). Moreover, *Mycoplasma* spp. leads to chronic pneumonitis in selected CVID patients. In addition to bacterial infections, CVID patients are also susceptible to respiratory viral infections but in the majority of patients, these viruses are not well studied (3). However, it is suggested that rhinoviruses are more frequent than immunocompetent individuals and last for a longer period (10). Severe pulmonary complications of varicella-zoster virus, herpes simplex, and cytomegalovirus infection have also been reported in a minority of CVID patients and in specific genetic defects associated with this phenotype. Although some published reviews have addressed CVID pulmonary complications, there are no specific publications to link the comprehensive pulmonary complications of each known CVID genetic defect and emphasize which monogenic patients have susceptibility to which type of respiratory manifestations.

Main Monogenic Causes of CVID

The current opinion about the pathogenesis of CVID is that heterogeneous etiologies can be underlying this phenotype and at least one-third of patients may be affected by a single genetic mutation in various genes (1,11). In recent years, several immunological defects as intrinsic and extrinsic B-cell signaling pathways have been identified in CVID cases that underwent next-generation sequencing (12). The chance of finding monogenic causes is higher in families with two or more members affected by CVID, but most unsolved cases are sporadic worldwide. In most patients with CVID, the genetic cause remains undefined due to a lack of resources or not yet identified novel genetic defect(s) (3,6). However, in genetically solved patients, the most common genetic causes of CVID are mutations in the genes encoding the proteins in cell signaling associated with surface molecules (e.g. B-cell receptor complex, T-helper cells and other costimulatory proteins), cytoplasmic molecules [e.g. guanine nucleotide exchange factors, phosphoinositide 3-kinases (PI3K) and other intracellular signal-regulated kinases] and nuclear molecules [e.g. transcription factors (TFs), nuclear factor kappa-light-chain-enhancer of activated B-cells (NF-kB) and DNA repair pathways] (13,14).

Some cases of monogenic CVID are inherited in an autosomal recessive manner, which means that a person must inherit two copies of the mutation (one from each parent) to develop the disorder (1). The main genes in this category are *LRBA, CD27/70* and *TNFRSF13C* genes, and they are mainly reported from countries in the Middle East and North Africa, with a higher rate of consanguineous marriage in this region (15,16). However, other common forms of CVID are inherited in autosomal dominant form (e.g., *TNFRSF13B*, *NFKB1/2*, *PIK3R1/CD*, *CTLA4, IKZF1* genes) and are more frequently reported in Western countries' cohorts of CVID patients (6,13). Immunological phenotypes differ between individuals with monogenic CVID based on the mutant gene as the impacted molecule can change the quality and quantity of immune response and inflammatory reactions (17). Subsequently, these variable immunologic properties might change the clinical presentation and particularly pulmonary manifestations of these patients in the context of each genetic defect (11).

In the next section, we sought to present an updated overview of the influence of monogenic abnormalities on infectious and non-infectious pulmonary manifestations and their consequences in the outcome of monogenic diseases linked to the CVID phenotype. The next sections will go into more detail on the abrogated molecules in these monogenic entities of CVID, their function and the affected developmental pathway, and the ensuing abnormalities in the development of pulmonary complications. The main pulmonary abnormalities seen in the majority of reported patients with monogenic CVID are summarized in Table 1 and Figure 1.

Pulmonary Complications of Monogenic CVID

BCR Signaling and Related Defects

The Ig transmembrane receptor protein known as B-cell receptor (BCR) is found on the surface of B-cells and is involved in the induction of adaptive immune responses. In the initial phase of B-cell development, memory

Table 1. Known monogenic human inborn errors of immunity with CVID phenotype associated with pulmonary complications

Monogenic defects with CSR impact	Function	URI*	LRI**	COVID-19 severity	Atopy***	Autoimmunity	Lymphoproliferation*****	Malignancy	Non-immune complications
BCR pathway									
CD19/CD81/CD21 (CR2)	LOF	++	+						
Tfh-related and other co-stimulatory factors									
ICOS/ICOSL	LOF	++	++	++		++			
CD27/CD70	LOF	++	++	++		++	+	+	
IL21/IL21R	LOF	++	+	++		+			
CTLA4/LRBA/DEF6	LOF	++	+	+++		++	+	+	
TNFRSF13C(BAFFR)	LOF	+	+			+			
TNFRSF13B(TACI)	LOF	+	+	+		+			
TNFSF13 (APRIL)	LOF	++	+	+					
TNFSF12 (TWEAK)	LOF	++	+						
CD20 (MS4A1)	LOF	++	+			+			
Cytoplasmic pathways									
VAV1	LOF	+	+						
RAC2	LOF	++	++		++	++			
ARHGEF1	LOF	++	+						
PIK3CD	GOF	++	+++	+		++	++	+++	Developmental delay
PIK3R1	LOF	++	+++	+		++	++	+++	Developmental delay
PIK3CG	LOF	++	++		++	++	+++		
PTEN	LOF	++	++			++	++	+	Developmental delay
PRKCD	LOF	++	++	+		++	++	+	
PLCG2	GOF	++	++		+++	++	+		
ATP6AP1	LOF	++	+						
SH3KBP1 (CIN85)	LOF	++	+						
MNOG	LOF	++	+						
SEC61A1	LOF	++	+						
Nuclear and other TFs pathways									
NFKB1	LOF	++	++	+		++	+	+	
NFKB2	LOF	++	++	++		++	+	+	
IKZF1	LOF	++	++			++		++	
IRF2BP2	LOF	++	+			++			
CTNNBL1	LOF	++	++			+	++		

LOF: Loss-of-function, GOF: Gain-of-function
*Including sinusitis, otitis media, chronic cough, tonsillitis, pharyngitis, laryngitis, epiglottitis, infectious mononucleosis
**Including pneumonia, bronchitis, empyema, purulent pleuritis, bronchiectasis, organizing pneumonia
***Including allergic rhinitis, asthma, hyperreactive diseases
****Including pulmonary autoimmune diseases including Churg-Strauss, Wegener, sarcoidosis, autoimmune rheumatologic induced pulmonary manifestations, idiopathic interstitial lung disease,
*****Including hilar lymphadenopathy, granulomatous lesions, granulomatous and lymphocytic interstitial lung diseases (GLILD)

recall activation, cytoskeletal reorganizations, pathogen reorganization, and antigen endocytosis, BCR activation is crucial (6). According to previous clinical studies, despite the normal number of B-cells in the periphery, a selected group of monogenic patients with CVID had faulty BCR activation. BCR activation is associated with several membrane receptors or co-stimulators, which are involved in the signal transduction cascade (17). The defective BCR

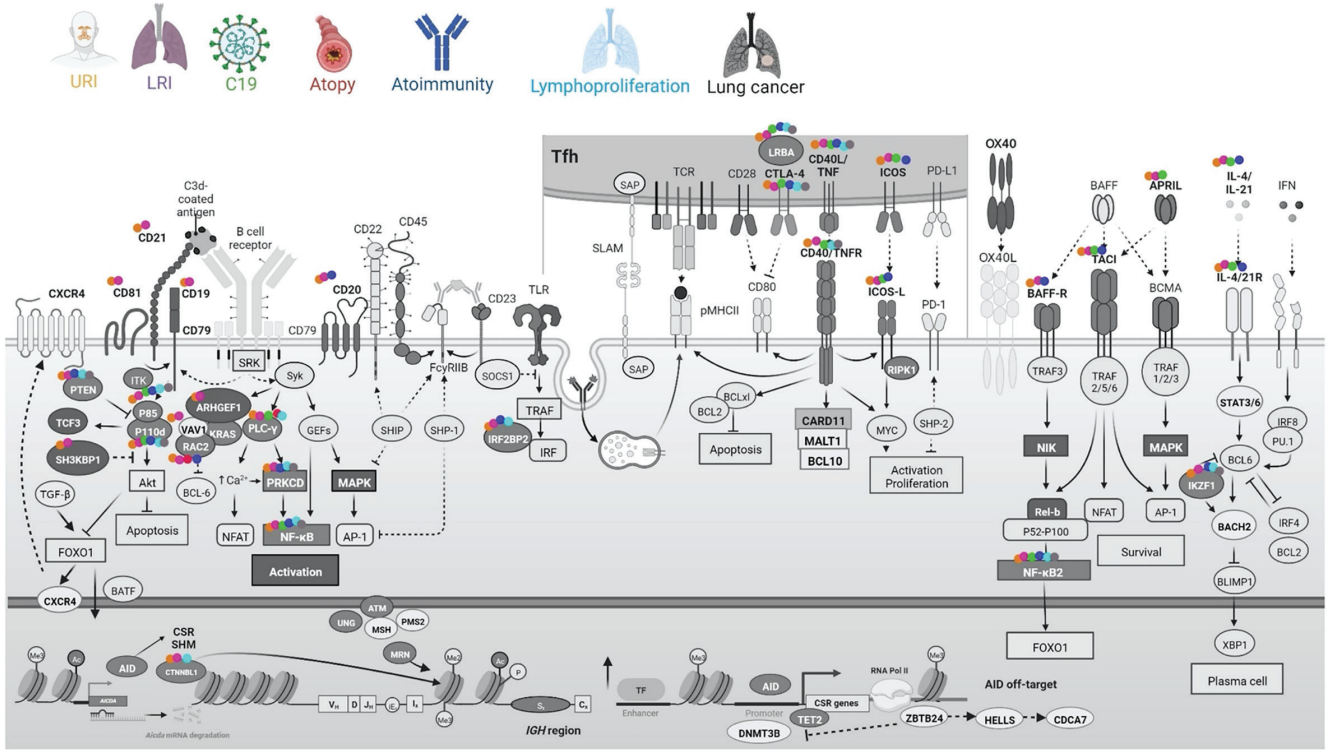

Figure 1. Schematic presentation of function of known monogenic human inborn errors of immunity with CVID phenotype associated with different pulmonary complications
CVID: Common variable immunodeficiency

signaling in these monogenic CVID patients is thought to result in an alteration in the terminal signaling of B-cells. Therefore, defective BCR complexes or BCR-mediated signaling molecules may contribute to the etiology and progression of CVID, mainly due to the dysfunction of BCR signal transduction for B-cell re-activation and late-differentiation. The B cell co-receptor complex, which is composed of CD19, CD21, and CD81 signals synergistically with the BCR following antigen interaction and lowers the threshold for receptor-dependent signaling (13). Because of this important function, mature B-cells in CVID patients with CD19-CD21-CD81 complex gene abnormalities do not respond properly to antigenic stimulation. On the other hand, CD21 also has an important role in B-cell proliferation and differentiation as complement receptor type 2 (CR2). The major ligands of CD21 are C3 fragments (specifically, C3d). Even though several studies have suggested C3d's contribution to humoral immunity, it appears that this is only true in animal models but not humans (18).

Currently reported patients with these genetic defects are very rare and the majority presented with recurrent otitis media and sinusitis as common signs/symptoms and other non-infectious pulmonary complications were not reported (Table 1). Inflammation of the middle ear in these patients can cause ear pain, hearing loss, and discharge from the ear. Chronic sinusitis also can lead to facial pain and pressure, nasal congestion, and difficulty breathing through the nose in these monogenic disorders. The diagnosis of otitis media and sinusitis in these entities of CVID patients can be challenging, as the symptoms can be similar to those of other CVID-related respiratory disorders. Imaging studies, such as computed tomography (CT) scans, may be used to confirm the diagnosis (9). Treatment options for otitis media and sinusitis in these patients typically include antibiotics to treat and prevent infections, decongestants to help clear nasal congestion, and pain relievers to alleviate symptoms. In addition, regular Ig replacement therapy and other immunomodulatory treatments (in case of recurrent upper respiratory infection and chronic sinusitis non-specific immunomodulators like non-steroidal anti-inflammatory drugs or topical/oral steroids and targeted immunomodulators like anti-IL-5 therapy with mepolizumab, reslizumab and anti IL-4/IL-13 with dupilumab) may also be used to improve the condition (10,19).

Follicular Helper T-cell Signaling and Costimulatory Molecules Defects

The proliferation, differentiation, and survival of B are tightly dependent on the co-stimulation from follicular T-lymphocytes (Tfh), follicular dendritic cells and other cytokines/chemokines in the microenvironment of secondary lymphoid organs/germinal center. Patients with

CVID have been shown to have several T and B-cells abrogated costimulatory molecules [except the crucial proteins for class-switching recombination (CSR) like CD40/CD40 ligand] (14,18).

It has been shown that patients with CVID have defects in the expression of specific Tfh costimulatory molecules, such as tumor necrosis factor (TNF)/TNF receptor superfamily (TNFRSF) including CD70 in B-cells and CD27 (as its ligand) in T-cells (6,20-24). As defects in the Tfh costimulatory signals' hints may be the cause of impaired B activation as well as defective amplification of the BCR-dependent signal transduction in CVID patients, mutations in these costimulatory molecules play a crucial role in defective delivering functional signals to both B and even Tfh-cells (14). Other important molecules in this pathway are IL-21/IL-21R and ICOS/ICOSL as individuals with these defects have more severe immune dysregulation resembling complicated CVID and also have reduced T-cell effector functions, impaired B-cell class-switching, and variable natural killer cell dysfunctions (25). Numerous recently published studies have demonstrated that individuals with CVID have a deficient expression of CTLA-4, DEF6 and LRBA in T-cells, particularly regulatory T-cells (26-30). Additionally, even newly discovered polymorphism in these genes in a subset of CVID patients is considered a risk factor for late-onset CVID (13,26).

In recent years, studies on independent T-cell co-stimulatory factors have indicated that patients with CVID can carry genetic mutations within effective molecules such as BAFFR, TACI, APRIL and TWEAK (6,31). The TNF receptor superfamily member 13B (*TNFRSF13B*) gene encodes a cell membrane receptor called a transmembrane activator and calcium-modulating cyclophilin ligand interactor (TACI) (6). TACI is mostly expressed on the surface of B-cells and plasma cells. The tailored function of TACI induces T-independent B-cell differentiation, isotype CSR, and Ig production. The TFs nuclear factor of activated T-cells (NFAT), activator protein 1 (AP1), and NFkB, as well as other TFs, are activated when TACI binds to its ligands, a proliferation-inducing ligand (APRIL) and B-cell-activating factor (BAFF) (13). This results in the induction of isotype switching to IgA and IgG in naive B-cells (31). B-cell stimulation, survival, and development are regulated by this receptor. B-cell growth and activation are also regulated by the BAFFR and it is crucial in the induction of CSR in B-cell (18). The PI3K pathway, which has been linked to B-cell growth and proliferation, is also activated by BAFF-R signaling. Several lines of evidence suggest that BAFF signaling is not necessary for all B cell subsets to survive or mature. Although B1 B-cells (found in mice, not humans) and switched memory B-cells may survive in the absence of BAFF signaling, it appears that follicular and marginal zone B-cells are strongly dependent on BAFF signaling (31).

TNF ligand superfamily member 13 (TNFSF13), also known as A proliferation-inducing ligand (APRIL), can crucially influence the synthesis of Ig and the development of memory B-cells into plasma cells (32). As a result, it is assumed that *TNFSF13* mutations are linked to poor plasma cell differentiation and Ig synthesis resembling CVID. Moreover, TNF ligand superfamily member 12 (TNFSF12), also known as TNF-like weak inducer of apoptosis (TWEAK), plays a part in BAFF signaling and B-cell survival (6,33). Because of its interaction with BAFF and down-regulation of the non-canonical NFkB pathway, *TNFSF12* mutations are therefore predicted to prevent BAFF-dependent B-cell survival and proliferation as well as Ig-CSR (18). On the other hand, CD20 also has an important role in B-cell proliferation and differentiation as a membrane-spanning 4A gene (MS4A). The ligand of CD20 is not identified yet but its expression is required for optimal B-cell immune response, specifically against T-independent antigens (6,17). Even though several studies have suggested that CD50 acts as a calcium channel to humoral immunity, it appears that this is only true in specific microenvironmental interactions including CXCR4/CXCL12 chemokine signaling. CVID subjects with CD20-deficient B cells displayed hypogammaglobulinemia and fewer class-switched memory B-cells (reduced IgG and IgA) (34).

Pulmonary complications are more diverse in this group of monogenic disorders. Due to the defective cellular immunity, the rates of lower respiratory infections and severe pneumonia are higher as well as complication of upper respiratory infections including hearing loss, tympanic membrane perforation, cholesteatoma, tympanosclerosis, mastoiditis, petrositis, labyrinthitis, and even meningitis (Table 1). Moreover, among non-infectious complications, rheumatologic autoimmune pulmonary manifestations, mixed connective tissue diseases and idiopathic interstitial lung diseases (ILD) can occur with higher frequency (35,36). In the context of ILD, patients suffer from chronic inflammation and scarring of the lung tissue, which can lead to difficulty breathing, cough, and fatigue. Moreover, bronchiectasis characterized by the abnormal widening and damage of the airways in the lungs can be observed frequently in this group of monogenic patients (37). It can impact the quality of life and lifespan of these patients considerably through chronic coughing, wheezing, and shortness of breath as well as respiratory failure. Individuals with ICOS/ICOSL, CD27/CD70, and CTLA4/LRBA/DEF6 deficiencies have a higher risk of

developing bronchiectasis due to recurrent respiratory infections and chronic inflammation of the airways. The exact cause of bronchiectasis in these patients is not fully understood, but it is believed to be related to recurrent respiratory infections and chronic immune dysregulation. Recurrent infections can cause damage to the airways and make them more susceptible to infection. Additionally, chronic inflammation can lead to a thickening of the airway walls, which can cause the airways to become narrowed and blocked and over a long time, may lead to cryptogenic organizing pneumonia (38). Treatment options for bronchiectasis typically include prophylactic antibiotics, bronchodilators, and mucolytic agents to help clear mucus from the lungs. In addition, immunoglobulin replacement therapy and other immunomodulatory treatments may also be used to improve chronic inflammation. Moreover, regular monitoring of lung function and screenings for bronchiectasis are necessary for these specific monogenic CVID patients (9). Atopic manifestations and particularly hyperreactive airway disease can also be documented in selected patients with CD27/CD70, and CTLA4/LRBA/DEF6 deficiencies. These patients may be characterized by increased airway responsiveness and bronchoconstriction (narrowing of the airways) in response to various stimuli, such as exposure to an unknown allergen. Some individuals with these monogenic forms of CVID may also manifest as asthma, bronchitis, or chronic obstructive pulmonary disease associated with chronic cough, wheezing, and shortness of breath. Additional therapeutic agents can help the management of this group of atopic cases and typically bronchodilators, and inhaled corticosteroids may be considered (38).

Cytoplasmic Molecules and Related Defects

BCR signal must be transduced to nuclear TF via cytoplasmic mediators' tyrosine kinases (TK) and subsequently guanine nucleotide exchange factors (GEFs) (6). GEFs in B cells include VAV1 which is mainly, if not entirely, expressed in hematopoietic-derived cells. Direct tyrosine phosphorylation downstream of BCR controls the activity of the VAV1-GEF when the ligand binds to these cell surface receptors that are either directly linked to TKs or activate cytosolic TKs in response to extracellular stimuli (39). The PH domain of VAV1 interacts with two lipid products of PI3K (18). Moreover, the auto-phosphorylated tails of receptor TKs connect directly with the SH2 domain of VAV1 in the cytoplasm to activate the protein (40). Through the activation of Rho-family guanosine triphosphate (GTPases), VAV1 controls a variety of cellular processes and signaling pathways in B-cells, as well as T-cells, natural killer cells, and osteoclasts. These include the transcription of genes, the maturation and activation of B-cells, and the rearrangement of the actin cytoskeleton. Many VAV1-driven processes, including the development of the immunological synapse and integrin clustering, are mediated by actin remodeling (39). The *RAC2* gene encodes Ras-related C3 botulinum toxin substrate 2, a GTPase that is only expressed on hematopoietic cells and is the main member of the Rac subfamily GTPases in B-cells. RAC2 sets the signaling molecules that bind to downstream effectors of VAV1 to govern a wide range of physiological activities, such as the regulation of cell growth, cell cycle, actin cytoskeleton remodeling, gene transcription, and the activation of protein kinases mainly PLCG2 (40). The *ARHGEF1* gene produces the Rho guanine nucleotide exchange factor 1 (ARHGEF1) protein, which is a member of the GEF family. RhoA guanosine triphosphatases and RAS superfamily proteins are both regulated by ARHGEF1-GTPase. Decreased RhoA activity and low cortical F-actin polymerization were seen in lymphocytes with the defective ARHGEF1 resembling CVID (41). ARHGEF1 is responsible for controlling the dynamics of the actin cytoskeleton, limiting PI3K/AKT signaling in B lymphocytes and facilitating the Ig-CSR process (13).

When the abovementioned pathways are activated downstream of BCRs, phosphatidylinositol 3,4-bisphosphate (PIP2) is converted into active phosphatidylinositol 3,4,5-triphosphate (PIP3), which is crucial for the regulation of immune cell growth, proliferation, trafficking, differentiation, and survival. The PI3Kδ pathway becomes more active because of heterozygous gain-of-function (GOF) mutations in the *PIK3CD* gene (APDS1) or loss-of-function mutations in the *PIK3R1* gene (APDS2). The ensuing defects in B-cell (and potentially Tfh cell) development in these patients mirror the CVID phenotype. The hyperactive PI3K downstream signaling cascade (PI3K/AKT/mTOR signaling pathway) may hamper proper terminal B-cell development and class switching step. PIP3 can also be produced when PI3Kγ phosphorylates PIP2 (42). This *PI3KCG* gene product is the second messenger that controls several signaling cascades involved in cell growth, proliferation, motility, and survival as well as cellular responses to growth factors, cytokines, chemokines, and antigen receptor activation. The tumor suppressor gene that codes for phosphatase and tensin homolog (PTEN) is also essential for PI3K pathway regulation. Through the activation of the forkhead box transcription factor 1 (FOXO1), PTEN reduces PI3K/AKT signaling (18). The generation of mature B-cells and response to multivalent antigens are induced by the activation of FOXO1 and PI3K suppression of PTEN. Somatic hypermutation (SHM) and CSR occur in the germinal center (GS) and are essential for the production of high-affinity antibody isotypes governed by balanced PI3K and FOXO1 crosstalk. Additionally, FOXO1 helps B-cells become localized to the GC. Due

to the loss of PI3K regulation in PTEN-deficient B-cells, adequate amounts of IgA and IgG isotypes cannot be produced resembling the immune profile of CVID (13).

Other main cytoplasmic molecules whose defects have been identified in CVID patients are associated with the specific physiologic condition of B-cells mainly due to antibody production and rapid cellular changes required for massive Ig expression. Recent genetic studies indicated ATP6AP1 deficiency (defect in luminal acidification of secretory vesicles), TRNT1 deficiency (defects in tRNA precursors), SH3KBP1 (CIN85) deficiency (defects in vesicle trafficking, cytoskeleton remodeling, and ubiquitinoylation-dependent activation, mannosyl-oligosaccharide glucosidase (MNOG) deficiency (defects in processing N-linked glycoproteins) and SEC61A1 deficiency (defect in membrane channel facilitating the translocation of proteins across endoplasmic reticulum membrane) can be presented with CVID immunologic phenotype (1,13).

Besides significant upper and lower infections and atopic and autoimmune ILD manifestations, pulmonary adenopathies and granulomatous disorders are more prevalent complications in patients with this group of monogenic defects (Table 1). Enlargement of the lymph nodes in the lungs and also malignancies including Hodgkin lymphoma can be observed in cases with dysfunctional PI3K pathway (9,43). In these CVID patients, pulmonary adenopathies can be caused by CSR defects adn uncontrolled proliferation of GC B-cells as well as recurrent infections and chronic inflammation and preset with chest pain, difficulty breathing, and a cough (38). The diagnosis of pulmonary adenopathies, granulomatous lesions and malignancies in CVID patients can be challenging and often requires a combination of imaging studies and biopsy (43). Treatment options for these patients will depend on the specific condition and may include surgery, radiation therapy, chemotherapy and even hematopoietic stem cell transplantations (42,44).

Nuclear Molecules and Transcription Factor Defects

NFkB was first discovered as a group of transcription factors that bind to the enhancer of the gene encoding the Ig-light chain. Recent advances in experimental studies have indicated that NFkB is essential for the growth, survival, and activation of B-lymphocytes, even though it involves the regulation of CSR and SHM (6,13). The canonical pathway, which regulates inflammatory responses (mainly short-term signals), and the non-canonical pathway, which is involved in immune cell differentiation and maturation (mainly long-term continues signals), as well as secondary lymphoid organogenesis, have been identified as two unique NFkB signaling pathways. The non-canonical NFkB route is described as not requiring NFkB essential modulator (NEMO), in contrast to the canonical pathway, which is defined as being mediated by an Inhibitory kappa B Kinases (IKK) that is NEMO-dependent (14).

It is widely known that a variety of external stimuli of B-cells, mainly BCR activation during inflammation, immunological response, cell proliferation, differentiation, and survival cause the canonical NFkB1 (p105/p50) activation. In order to change the form from p105 of the TF/p50 which can go to the nucleus and activate the target genes, the inhibiting IkB proteins are phosphorylated and exposed to ubiquitination-dependent destruction by the proteasome. However, the non-canonical NFkB is only activated by a small number of TNF superfamily co-stimulators, suggesting that the biological purposes of this branch of the pathway are more narrowly focused. The primary kinase in this pathway, NFkB-inducing kinase (NIK), is kept below the detectable level in the steady-state condition by TNF receptor-associated factors (TRAFs), which is required for ubiquitination-mediated degradation. Temporary generation of NIK can release active dimer by phosphorylating NFkB2 (p100), which is then converted to p52 and translocated into the nucleus to activate the target gene by NIK and IKK.

IKAROS, a zinc finger IKZF1 transcription factor, is an essential hematopoiesis regulator. It is necessary for the early formation of B-cell progenitors and, at a later stage, for VDJ recombination and the production of BCR. In order to determine the appropriate antibody isotype during CSR and to adjust the activation threshold for varied stimuli, mature B-cells depend on IKZF1 (14). This TF thus participates in practically all aspects of B-cell development and function and may lead to CVID phenotype if mutations lead to haploinsufficiency. Defects in other crucial nuclear elements can also manifest with CVID phenotypes among which IRF2BP2 deficiency (Interferon regulatory factor 2-binding protein 2 belongs to a family of proteins that regulate transcription of type I interferon) and CTNNBL1 deficiency (abrogated AID-interacting protein through which it participates in SHM as well as CSR) are discovered recently (13). Pulmonary complications of this group of monogenic forms of CVID are as severe as cytoplasmic molecular defects mentioned in the previous section with diverse presentations of recurrent/severe infections, autoimmune ILD, and lymphoproliferation; however, the rate of respiratory atopic manifestations is lower in patients reported with these genetic defects (Table 1).

COVID-19 Pulmonary Complications in Monogenic CVID

Since CVID is the most prevalent symptomatic inborn error of immunity (3), viral infections and particularly

COVID-19 can be more frequently diagnosed in these patients. Therefore, it is particularly intriguing to estimate the prognosis of SARS-CoV-2 infection in different monogenic forms of CVID (45,46). While the majority of those infected with the virus are asymptomatic or only experience mild to moderate symptoms, a small percentage of CVID patients experience severe to life-threatening symptoms (for instance, acute respiratory distress syndrome and severe hypoxemia), which can sometimes be deadly (45). Numerous COVID-19 instances in CVID patients have been documented thus far, with both non-serious and serious infection outcomes, but the molecular defects in patients with the severe condition are not well-described. Although there are little rigorous cohort-wide data, many published articles focus on single case reports of hospitalized patients (47-72).

The most common COVID-19 symptoms in CVID patients, including fever, cough, and dyspnea, are similar to the immunocompetent population; however, myalgia, fatigue, and intestinal problems are observed in higher incidences (73). The risk of hospitalization is increased among CVID patients compared to the normal population, especially in cases with immunosuppressive therapy, cardiovascular complications and chronic lung disease. Vaccination of more than 3 doses can shorten the acute phase of infection with COVID-19 in CVID cases but it does not have an impact on hospitalization, especially during Omicron variants of concern wave (74). Secondary bacterial super-infections in COVID-19-carrying CVID patients may perhaps be more of a worry than SARS-CoV-2 itself (75,76). This phenomenon is more expected in cases with pre-existing chronic pulmonary problems accompanied by immunological inflammation (e.g. immune dysregulation in the context of bronchiectasis or ILD), who need more special attention in their management throughout the ongoing pandemic (77). Therefore, CVID patients require more intense treatment including antibiotics, immunomodulatory and anti-inflammatory (e.g. chloroquine/hydroxychloroquine), antiviral therapy (e.g. lopinavir, ritonavir, and remdesivir, nirmatrelvir, molnupiravir), higher doses of Ig-, and monoclonal antibodies therapy (such as tocilizumab, IL-6 inhibitors to decrease lung macrophages hyperactivation) (47,73,76). A recent multicenter study showed that CVID patients infected following the dissemination of the Delta variant responded well to home-based monoclonal antibodies therapy; however, neither monoclonal antibodies nor antivirals were shown to reduce the probability of hospitalization during the Omicron wave (74). Most reports of monoclonal antibody effectiveness decline during the Omicron wave have focused on the more recent sub-variants (78,79). When taken as a whole, the home care approaches decreased the chance of hospital admission during the Omicron period (74). Of note, the beneficial effects of convalescent plasma application have been proven also in the majority of CVID patients with severe COVID-19 (46). Post-infection (anti-nucleocapsid) seroconversion was found in the majority of the CVID individuals who underwent evaluation. Different types of immunization were demonstrated to be well tolerated in these cases but postimmunization anti-spike serology was positive in a minority of CVID patients (the majority of cases fail to produce a sufficient humoral response) (75). Reinfection despite vaccination (breakthrough infection mainly due to omicron infection) is also recorded in CVID cases in a higher frequency (~3-fold) compared to the immunocompetent population (74). Whether a natural infection before vaccination increases the incidence of seroconversion after immunization is a related concern about vaccine effectiveness in people with CVID. Although the genetic defects are not defined, when compared to the overall infection-fatality rates across human populations, the proportions of moderately to seriously (~25-40%) and critically infected individuals (~20-25%), as well as those who died from COVID-19-related sequelae (~5-15%) are slightly higher among CVID patients. These comparisons, nevertheless, could lead to overestimations as asymptomatic or mild COVID-19 infections in CVID patients-which certainly occur-are mostly disregarded (45,47,73,76).

For the monogenic CVID groups, ongoing assessment of the clinical outcomes of individuals is required to produce risk-modifying recommendations. Due to the diversity of each CVID patient's underlying immunological weakness, it should be kept in mind that each patient's cellular and humoral responses should be investigated individually. Table 2 summarizes currently reported COVID-19 patients with CVID genetic defects, suggesting that the majority of these molecular defects course and mortality risk appear to be comparable to that in patients with SARS-CoV-2 infection without CVID. In people with monogenic CVID, there is also a slightly greater risk (25%) of moderate to severe COVID-19 infections, with a 5.5% fatality rate (reported in CTLA-4 and NFKB2 deficiencies). These findings are in contrast to several earlier reports that indicated milder COVID-19 infections, and they may be explained by the presence of comorbidities and risk factors, heterogeneity in viral load, genetic predispositions, a wide variety of viral strains, and certain case-report limitations. Future research using bigger cohorts is required to keep track of COVID-19 results in monogenic-CVID individuals. Because asymptomatic individuals are less likely to be identified and thus reported, our findings on monogenic CVID patients may be biased in favor of COVID-19 infections that are more severe. Importantly, to stop the COVID-19 pandemic, effective SARS-CoV-2

Table 2. Summary of monogenic CVID patients with COVID-19 reported in the literature to date

Monogenic diagnosis	Gender/Age	Outcome	Reference
Tfh-related and other co-stimulatory factors			
ICOS deficiency	Female/adult	Moderate/recovered	PMID: 33338534
ICOS deficiency (n=2)	2 females/32.5 (28.0-37.0)y	1 severe/recovered	PMID: 35641155
CD70 deficiency	Female/372m	Moderate/recovered	PMID: 33263173
CD27 deficiency	Male/20m	Severe/recovered	PMID: 37002625
IL21R deficiency	Unknown/21y	Severe/recovered	PMID: 34510555
CTLA4 deficiency	Female/15y	Moderate/recovered	PMID: 32980424
CTLA4 deficiency	Unknown/30y	Moderate/recovered	PMID: 32980424
CTLA4 deficiency	Female/59y	Mild/recovered	PMID: 33519822
CTLA4 deficiency	Male/17y	Mild/recovered	PMID: 34034269
CTLA4 deficiency	Male/adult	Severe/died	PMID: 33338534
CTLA4 deficiency	Unknown/unknown	Mild/persistent infection	PMID: 34971385
CTLA4 deficiency	Male/adult	Severe/died	PMID: 35641155
LRBA deficiency	Male/20y	Mild/recovered	PMID: 32980424
LRBA deficiency	Female/59y	Asymptomatic	PMID: 33519822
LRBA deficiency	Male/29.7y	Mild/recovered	PMID: 34314546
LRBA deficiency	Male/12y	ICU admission/recovered	PMID: 34521740
LRBA deficiency	Male/30y	Mild/recovered	PMID: 34231093
LRBA deficiency	Female/46y	ICU admission/died	PMID: 34231093
LRBA deficiency	Male/14y	Severe/recovered	PMID: 35490276
TACI deficiency	Female/29.1y	Mild/recovered	PMID: 34314546
TNFSF13 (APRIL) deficiency	Female/9y	Recovered	PMID: 34114122
Cytoplasmic pathways			
PI3KCD gain-of-function	Male/13.1y	Asymptomatic/recovered	PMID: 34164762
PI3KCD gain-of-function	Male/24y	Asymptomatic	PMID: 35445287
PI3KCD gain-of-function	Male/25y	Moderate/recovered	PMID: 36003051
PIK3R1 deficiency	Female/30y	Asymptomatic-mild	PMID: 32980424
PIK3R1 deficiency	Male/4y	Severe/recovered	PMID: 35707532
PI3KCD/PIK3R1	Male/15y	Mild or moderate/recovered	PMID: 35445287
PI3KCD/PIK3R1 (n=3)	2 females and 1 male/42 ± 16y	Mild/recovered	PMID: 35296097
PRKCD deficiency	Male/10y	Recovered	PMID: 32980424
Nuclear and other TFs pathways			
NFKB deficiency (n=2)	2 males/30.5 (27.0-34.0)y	2 recovered	PMID: 33338534
NFKB1 deficiency	Male/40y	Mild/recovered	PMID: 32980424
NFKB1 deficiency	Female/60y	Mild/recovered	PMID: 32980424
NFKB1 deficiency	Female/61y	Mild/recovered	PMID: 33039649
NFKB1 deficiency	Male/38y	Mild/recovered	PMID: 33039649
NFKB1 deficiency	Male/40y	Mild/recovered	PMID: 36003051
NFKB1 deficiency	Female/59y	Moderate/recovered	PMID: 36003051
NFKB1 deficiency (n=2)	2 males/34 (27.0-41.0)y	1 severe/recovered	PMID: 35641155
NFKB2 deficiency	Male/40y	ICU admission/recovered	PMID: 32980424
NFKB2 deficiency	Male/15y	ICU admission/recovered	PMID: 32980424
NFKB2 deficiency	Male/15y	Hyperinflammatory/ICU admission/recovered	PMID: 33007327
NFKB2 deficiency	Female/30y	Severe/recovered	PMID: 34893946
NFKB2 deficiency	Female/32y	Mild/recovered	PMID: 34929372
NFKB2 deficiency	Female/adult	Severe/died	PMID: 35641155
NFKB2 deficiency	Unknown/9y	Mild/recovered	PMID: 34510555

NFKB2 deficiency	Female/unknown	Severe/recovered	PMID: 36509151
NFKB2 deficiency	Male/unknown	Mild/recovered	PMC10203942
NFKB2 deficiency	Male/unknown	Mild/recovered	PMC10203942
NFKB2 deficiency	Male/unknown	Mild/recovered	PMC10203942
NFKB2 deficiency	Male/unknown	Mild/recovered	PMC10203942
NFKB2 deficiency	Female/unknown	Mild/recovered	PMC10203942
NFKB2 deficiency	Male/unknown	Mild/recovered	PMC10203942

management in patients with immunodeficiency (mainly antibody deficient and CVID patients) is required as they can be potentially a prolonged reservoir of viruses and vaccination is not protective in these patients.

Authorship Contributions

Concept: S.D., H.H., Design: S.D., H.A., Data Collection or Processing: M.E., F.S., S.R., Literature Search: S.F., M.Y, N.F., Writing: S.D., H.A.

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