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Lymphoproliferative Disease in CVID: a Report of Types and Frequencies from a US Patient Registry

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Abstract

Purpose—Lymphoproliferative disease in common variable immunodeficiency disease (CVID) is heterogeneous in pathogenesis and ranges from non-malignant lymphoid hyperplasia to lymphoma.

Methods—The United States Immunodeficiency Network (USIDNET) patient registry was queried for lymphoproliferative diseases reported in CVID patients. Diagnoses included as possible manifestations of lymphoproliferation included lymphadenopathy, lymphoid hyperplasia, lymphocytic inflammation, lymphocytosis, and gammopathy.

Results—Among 1091 CVID patients, lymphoproliferative conditions were reported in 17.2% ($N = 188$). These conditions included lymphadenopathy ($N = 192$, 12.3%), lymphoid hyperplasia or lymphocytic inflammation ($N = 50$, 4.6%), lymphocytosis ($N = 3$, 0.3%), and gammopathies ($N = 3$, 0.3%). Of the 188 patients with lymphoproliferative conditions, 15 (8%) also had a diagnosis of lymphoma, while the remaining 173 (92%) did not. Nine (4.8%) had a diagnosis of non-lymphomatous malignancy including basal cell carcinoma ($N = 3$, 1.6%), thyroid carcinoma ($N = 2$, 1.1%), gynecologic cancer ($N = 2$, 1.1%), testicular cancer ($N = 1$), and vocal cord carcinoma ($N = 1$). CVID patients with lymphoma were older than patients with lymphoproliferative disease who did not have a diagnosis of lymphoma at the time of analysis (median age 49 vs. 35 years, $p = 0.005$). CVID patients with lymphoproliferative disease had 2.5 times higher odds of having chronic lung disease compared with those with lymphoma (OR = 0.4, $p = 0.049$). There were no significant differences in the frequency of autoimmune, gastrointestinal, hepatic, or granulomatous disease between these populations.

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Authorship Contributions Each author made substantial contributions to study concept and design, helped with data interpretation, drafted the article or reviewed or critically, and gave final approval of the version to be published. Dr. Cunningham-Rundles, Dr. Fuleihan, and Dr. Sullivan contributed a significant portion of the CVID patients to the USIDNET registry that were analyzed in this study. Dr. Yakaboski and Dr. Feuille carried out data analysis. Authors collectively have personally written 100% of the manuscript.

Conflict of Interest The authors declare that they have no conflict of interest.

Conclusions—While CVID patients are at increased risk for lymphoma, lymphoproliferation may be observed in the absence of a concurrent hematologic or solid tumor malignancy.

Keywords

CVID; common variable immunodeficiency; lymphoproliferation; lymphoproliferative disease; lymphoproliferative disorder; lymphoma

Introduction

Common variable immunodeficiency (CVID) is a heterogeneous group of disorders characterized by markedly reduced serum IgG with low IgA and/or IgM, as well as poor or absent specific antibody responses to immunization [1–3]. Absence of other defined immunodeficiency states or causes of hypogammaglobulinemia is an additional diagnostic criterion. CVID is the most prevalent symptomatic primary immunodeficiency disease (PIDD) in adults in the USA [4].

Although the practice of regular immunoglobulin replacement has decreased morbidity and mortality from infection in CVID patients, non-infectious comorbidities remain a significant burden on this population [5–7]. CVID patients have an inherently increased risk of lymphoproliferation ranging from non-malignant lymphoid hyperplasia to lymphoma. This lymphoproliferative disease is heterogeneous in nature with several contributing factors including impaired immunosurveillance, chronic infections, and genetic predisposition [8]. When compared with the age-matched general population, it has been shown that CVID patients have a higher incidence of lymphoma as well as leukemia, gastric cancer, and skin cancer [5, 9, 10]. Other known comorbidities of CVID include autoimmunity, interstitial lung disease, bronchiectasis, enteropathy, hepatic disease, and granulomatous disease [6, 7, 11].

The purpose of this study was to report the types and frequency of lymphoproliferative disease in CVID patients in the USIDNET registry, to report the frequency of having associated lymphoma or other malignancy occurring in association with lymphoproliferative disease, and lastly, to evaluate whether certain patient characteristics might be predictive of increased odds of having a diagnosis of lymphoma than with having lymphoproliferation alone.

Methods

The United States Immunodeficiency Network (USIDNET) registry is a multi-site registry of data from patients with primary immunodeficiency disease in the USA and Canada, formed in 2003 and funded by an NIH resource grant awarded to the Immune Deficiency Foundation. The registry was established to advance research in primary immunodeficiency disease and allows investigators to submit queries to obtain de-identified patient data for analysis.

For this study, the USIDNET registry was queried for lymphoproliferative disease as well as any other reported medical conditions, demographics, ages at diagnosis and at last data

entry, immunoglobulin (Ig) levels, infections, and genetics in CVID patients enrolled in the registry as of May 30, 2018. Patients with thymoma were excluded. Patients with genetic testing supportive of a primary immunodeficiency other than CVID were excluded. Lastly, for this study, we only included patients with evidence of at least one IgA or IgM value less than 2 standard deviations (SD) below the standard laboratory mean for age (for adults, IgA < 70 mg/dL; IgM < 40 mg/dL). We did not exclude patients with normal IgG levels as patients may have been on IgG replacement therapy at the time of registry enrollment, and baseline levels were not always reported.

For data on lymphoproliferative disease, all conditions were examined individually, and diagnoses that qualified as lymphoproliferative disease were classified into the following categories as listed in Table 1: gammopathies (monoclonal gammopathy and one patient who developed multiple myeloma), lymphocytic inflammation (lung-specific including follicular bronchiolitis, lymphoid interstitial pneumonia, and pulmonary nodular lymphoid hyperplasia; gastrointestinal-specific including lymphocytic-plasmacytic colitis and nodular lymphoid hyperplasia of the intestine; or not organ-specific including lymphoid hyperplasia, autoimmune lymphoproliferative syndrome, chronic lymphocytic inflammation, and relapsing febrile nodular non-suppurative panniculitis), lymphocytosis, and lymphadenopathy. Demographics, ages at diagnosis and at most recent data entry in the registry, autoimmune disease, and additional CVID-associated conditions were compared between patients with lymphoma and patients with lymphoproliferative disease without lymphoma. Specifically, autoimmune conditions that were compared between the two cohorts included autoimmune cytopenias (immune thrombocytopenia, autoimmune hemolytic anemia, autoimmune neutropenia, and Evans syndrome), systemic autoimmune conditions (rheumatoid arthritis, systemic lupus erythematosus, vasculitis, and others including mixed connective tissue disease, spondyloarthropathies, juvenile arthritis, dermatomyositis, and inflammatory polyarthropathies), and organ-specific autoimmune conditions (integumentary, including psoriasis, vitiligo, lichen planus, and alopecia areata; enteropathic, including autoimmune enteritis or celiac disease; autoimmune hepatitis; endocrine, including type 1 diabetes mellitus, thyroiditis; and ocular, including uveitis and iritis). Additional CVID-associated conditions that were compared between the two cohorts were categorized, as detailed in Table 3. Of note, it is unknown whether the diagnosis of CVID preceded or followed other diagnoses (including lymphoproliferation and lymphoma) in these patients.

Statistical Analysis

The demographics of patients with lymphoma were compared with those of patients with lymphoproliferative disease excluding lymphoma using “N-1” chi-squared test for categorical variables (MedCalc ® Software © 2017) and two-tailed, heteroscedastic t test for continuous variables (Microsoft ® Excel for Mac © 2018). The frequency of autoimmune disease and other CVID-associated conditions were compared between these two populations using the odds ratio with mid-P calculation (MedCalc ® Software © 2017) [12].

Results

In total, 1565 patients with a diagnosis of CVID were registered in the USIDNET Registry as of May 30, 2018. Nine with a diagnosis of thymoma and 11 with genetic testing supportive of PIDD other than CVID or genes with known increased susceptibility to oncologic/autoimmune disease were excluded. Specifically, 11 patients were excluded for the following gene mutations: *TRNT1*, *UNG* deficiency, *TNFRSF5*, *DEL22q11.2*, duplication of 22q11.2, *BTK*, *CREBBP*, *IFIH1*, *ARTEMIS*, *RAD50*, and *AIRE*. Another 454 subjects were excluded as they were without at least one IgM or IgA value < 2 SD below standard laboratory mean. After these exclusions, the analysis included 1091 patients.

Lymphoproliferative Disease in CVID

Of the 1091 CVID patients in this study, 188 (17.2%) had at least one diagnosis of lymphoproliferative disease (Table 1). The most commonly reported condition was lymphadenopathy ($N=150$; 13.7%), followed by lymphocytic inflammation ($N=50$; 4.6%), lymphocytosis ($N=3$; 0.3%), and gammopathy ($N=3$; 0.3%). Of those with lymphocytic inflammation, 23 (2.1%) had conditions that were lung-specific, 14 (1.3%) had conditions that were gastrointestinal-specific, and 18 (1.6%) had conditions that were not organ-specific. None of the patients was reported to have EBV infection.

Lymphoproliferative Disease and Cancer in CVID

Of the 188 CVID patients with lymphoproliferative disease, 15 (8.0%) also had a diagnosis of lymphoma, while 173 (92.0%) did not have a diagnosis of lymphoma reported at the time of analysis. Nine (4.8%) were diagnosed with solid tumors, including basal cell carcinoma ($N=3$, 1.6%), thyroid cancer ($N=2$, 1.1%), gynecologic cancer ($N=2$, 1.1%), testicular cancer ($N=1$), and vocal cord carcinoma ($N=1$).

Lymphoma in CVID

Of the total of 1091 patients with CVID included in this study, 45 (4.1%) carried a diagnosis of lymphoma (Table 1). Most commonly, the specific type of lymphoid neoplasm was not specified ($N=28$; 62.2%). Based on the WHO classification of lymphoid neoplasms [13], 11 (24.4%) had a mature B cell neoplasm, 5 (11.1%) had Hodgkin lymphoma, and 2 (4.4%) had a mature T cell neoplasm. One patient was reported to have both Hodgkin lymphoma and non-Hodgkin lymphoma. There were 7 (0.6%) CVID patients in the study without lymphoma or lymphoproliferative disease who had a diagnosis of leukemia. CVID patients with lymphoproliferative disease had 2.5 times increased odds of having a diagnosis of lymphoma than CVID patients without lymphoproliferative disease were ($p=0.005$).

Comparison of CVID Patients with Lymphoma and Those with Lymphoproliferative Disease

There were no significant differences in race ($p=0.139$, $p=0.396$, and $p=0.685$) or ethnicity ($p=0.828$, $p=0.448$ and $p=0.479$) between CVID patients with lymphoma and those with lymphoproliferative disease without lymphoma (Table 2). For both cohorts, the majority of patients were Caucasian and non-Hispanic. There were more males in the lymphoma cohort ($N=24$, 53.3%) and more females in the lymphoproliferative disease cohort ($N=89$, 51.4%); this difference was not statistically significant ($p=0.569$).

However, patients with lymphoma had a significantly higher age at CVID diagnosis (median age 33 years) and age at last entry (median age of 49 years) compared with those with lymphoproliferative disease without lymphoma (median age of 26 years and 35 years, respectively; $p = 0.005$ and $p < 0.001$, respectively.)

Autoimmune disease was reported in 14 (31.1%) of the 45 patients with lymphoma and in 61 (35.3%) of the 173 patients with lymphoproliferative disease (Table 3). There was no significant difference between the overall frequency of autoimmune disease between these two cohorts ($p = 0.602$), or of specific subtypes of autoimmune disease including autoimmune cytopenia ($p = 1.66$), systemic autoimmune conditions ($p = 0.272$), or organ-specific autoimmune conditions ($p = 0.775$).

When comparing additional CVID-associated comorbidities between patients with lymphoma and patients with lymphoproliferative disease, frequency of chronic lung disease was significantly higher in those with lymphoproliferative disease without lymphoma compared with those with lymphoma ($p = 0.485$) (Table 3). There were no significant differences in the reported frequency of enteropathy ($p = 0.828$), irritable bowel disease ($p = 0.591$), and hepatic disease ($p = 0.409$) between these two populations. Granulomatous disease was reported in 7 (4%) patients with lymphoproliferative disease, but was not in patients with lymphoma.

Genetic Testing

There were 50 CVID patients with genetic testing reported (Table 4). The most commonly reported gene mutation was *TNFRSF13B* ($N = 27$), followed by *NFKB2* ($N = 5$), *CD19* ($N = 3$), *TNFSF12* ($N = 2$), and *PIK3CD* ($N = 2$). Of these CVID patients with genetic testing, 2 had lymphoma (each with mutations in *TNFRSF13B*) and 13 had lymphoproliferative disease (8 with mutations in *TNFRSF13B*, and the remaining mutations in *NFKB2*, *PIK3CD*, *CTLA4*, *HLA-DQ*, and *SMC3*).

Discussion

Lymphoproliferative disease was reported in 17.2% of the 1091 CVID patients included in this study (Table 1). Although it has been shown that the prevalence of CVID-associated complications including lymphoproliferative disease varies among countries [6], lymphoid hyperplasia and splenomegaly are typically found in at least 20% of CVID patients [14]. The EUROclass trial reported lymphadenopathy in 26.2% and splenomegaly in 40.5% of 303 CVID patients studied [15].

A US-based study of 473 CVID patients found that lymphoma ($N = 39$; 8.2%) was the second most common cause of mortality in CVID, after chronic lung disease ($N = 135$; 28.5%) [7]. It has also been shown that of the patients carrying a diagnosis of CVID in the USIDNET, there was a higher incidence rate of lymphoma compared with the age-matched general population [9]. Of the 1091 CVID patients included in our study, lymphoma was reported in 4% ($N = 45$) (Table 1). These findings are consistent with those of previous studies showing that lymphoma occurs in an estimated 2–8% of CVID patients [11] and that the majority are non-Hodgkin [16]. Of the 188 CVID patients with lymphoproliferative

conditions, lymphoma was reported in 8% ($N = 15$). These patients were significantly more likely to have a diagnosis of lymphoma compared with CVID patients without other lymphoproliferative conditions ($OR = 2.5$; $p = 0.005$).

When comparing CVID patients with lymphoma to CVID patients with other lymphoproliferative conditions, we found that patients with lymphoma had a significantly higher age at CVID diagnosis and age at last registry entry ($p = 0.005$ and $p < 0.001$, respectively.) These findings are consistent with previous studies that have shown CVID patients with older age of onset more often had lymphoma [17]. There was a significantly higher frequency of chronic lung disease in patients with lymphoproliferative disease ($N = 53$) when compared with patients with lymphoma ($N = 3$); this appears to be due to lymphoproliferative disease frequently manifesting in the lung on this cohort of patients, with 23 of 188 patients with lymphoproliferation reporting lung-specific lymphoproliferative conditions.

There was no significant difference in the frequency of autoimmune disease, gastrointestinal disease, and hepatic disease among CVID patients with lymphoma compared with those with other lymphoproliferative conditions without lymphoma (Table 3). Of these known CVID-associated complications, autoimmune disease was most commonly reported, occurring in 25% ($N = 268$) of CVID patients included in this study. This is comparable to previous studies showing autoimmunity in 25–30% of CVID patients [1, 5, 7, 14].

Of the 50 CVID patients with genetic testing included in our study, there were 15 mutated genes identified (Table 4). Of the mutated genes identified in this study, those that have been associated with monogenic CVID include *TNFRSF13B*, *NFKB2*, *CD19*, *TNFSF12* (TWEAK), *PIK3CD*, *NFKB1*, *CR2* (CD21), *ICOS*, *IRF2BP2*, and *CTLA4* [18]. Certain HLA haplotypes, including *HLA-DQ/DR*, have also been associated with susceptibility to CVID as modifier genes [18–20]. The remaining mutated genes reported in this study (*MTHFR*, *F5* (factor 5 Leiden), *SMC3*) are not associated with CVID to our knowledge and may represent incidental findings.

Limitations of our study include the exclusion of patients who did not have Ig levels reported in the registry. It is possible that the resulting decrease in N limited our ability to detect differences between the patients with lymphoma and those with lymphoproliferative disease. Additionally, as this was a registry-based study, there is no consensus on diagnostic criteria for the condition of lymphoma or other lymphoproliferative disease. Although we were able to report the age of CVID diagnosis for most patients in this study, we did not have data on age of disease onset, delay in diagnosis, and which co-morbidities were present at the time of CVID diagnosis vs. at follow-up.

In conclusion, while CVID patients are at increased risk for certain cancers compared to the age-matched population, lymphoproliferative disease may be appreciated in this population in the absence of concurrent hematologic or solid tumor malignancy. Those with lymphoma had older age at time of CVID diagnosis and at time of last registry entry, compared with those with lymphoproliferation without lymphoma. There were otherwise no significant differences between CVID patients with lymphoproliferative disease and those with

lymphoma. Future studies are needed to further assess if it is phenotypically or genetically possible to identify which CVID patients with lymphoproliferative disease may be at an increased lifetime risk of developing hematologic or solid tumor malignancy and thus warrant closer monitoring.

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Abbreviations

CVID	Common variable immunodeficiency
Ig	Immunoglobulin
PIDD	Primary immunodeficiency disease
SD	Standard deviation
TACI	Transmembrane activator and calcium-modulating cyclophilin ligand interactor
USIDNET	United States Immunodeficiency Network

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Table 1Lymphoproliferative conditions and lymphoma among 1091 patients with CVID in the USIDNET registry^a

Lymphoproliferative disease	N (%)
Any lymphoproliferative disease	188 (17.2)
Gammopathies	3 (0.3)
Multiple myeloma	2 (0.2)
Monoclonal gammopathy	1
Lymphocytic inflammation	50 (4.6)
Organ-specific: lung	23 (2.1)
Organ-specific: gastrointestinal	14 (1.3)
Not organ-specific	18 (1.6)
Lymphocytosis	3 (0.3)
Lymphadenopathy	150 (13.7)
Lymphoma	N (%)
Any lymphoid neoplasm	45 (4.1)
Hodgkin lymphoma	5 (11.1)
Mature B cell lymphoid neoplasm	11 (24.4)
Mature T cell lymphoid neoplasm	2 (4.4)
Lymphoid neoplasm NOS	28 (62.2)

NOS not otherwise specified

^aDiagnoses are presented as reported by contributors to the USIDNET registry. Of note, some patients were reported to have multiple lymphoproliferative conditions and one patient was reported to have both Hodgkin and non-Hodgkin lymphoma

Table 2

Demographics of CVID patients with lymphoma compared to those with lymphoproliferative disease in the USIDNET registry

		CVID cohort (N = 1091)	+Lymphoma (N = 45)	+LPD –lymphoma (N = 173)	* p
Gender, N (%)	Male	483 (44.3)	24 (53.3)	84 (48.6)	0.569
	Female	608 (55.7)	21 (46.7)	89 (51.4)	0.569
Race, N (%)	Caucasian	923 (84.6)	40 (88.9)	137 (79.2)	0.139
	African American	28 (2.6)	1	9 (5.2)	0.396
	American Indian	3 (0.3)	0	1	n/a
	Asian	6 (0.5)	0	3 (1.7)	n/a
Ethnicity, N (%)	Other or multiracial	18 (1.6)	0	4 (2.3)	n/a
	Not reported	113 (10.4)	4 (8.9)	19 (11.0)	0.685
	Hispanic	28 (2.6)	1	3 (1.7)	0.828
	Not Hispanic	619 (56.7)	28 (62.2)	118 (68.2)	0.448
Age in years	Not reported	444 (40.7)	16 (35.6)	52 (30.1)	0.479
	Age of diagnosis	28 (11–44)	33 (24–48)	26 (13–40)	0.005
Median (IQR)	Age at last entry	38 (19–54)	49 (42–61)	35 (22–50)	< 0.001

CVID Cohort all patients included in the study, +Lymphoma CVID patients with lymphoma, +LPD –Lymphoma CVID patients with lymphoproliferative disease, but not lymphoma, n/a p value cannot be calculated with at least one of the values being zero

* p value was determined using chi-square calculation (categorical variables) and Student's t test (continuous variables)

Patients with lymphoma had a significantly higher age of diagnosis and age at last entry than patients with lymphoproliferative disease ($p = 0.005$ and $p < 0.001$, respectively)

Table 3

Comparison of autoimmune disease and other comorbidities in CVID patients with lymphoma and those with lymphoproliferative disease in the USIDNET registry^a

	CVID cohort (N = 1091) N (%)	+Lymphoma (N = 45) N (%)	+LPD –Lymphoma (N = 173) N (%)	OR	95% CI	p [*]
Any autoimmune condition	268 (24.6)	14 (31.1)	61 (35.3)	0.8	(0.4–1.7)	0.602
Autoimmune cytopenia ^b	98 (9)	5 (11.1)	35 (20.2)	0.5	(0.2–1.3)	0.166
Systemic autoimmunity ^c	64 (5.9)	4 (8.9)	8 (4.6)	2	(0.6–7.0)	0.272
Organ-specific conditions ^d	143 (13.1)	6 (13.3)	26 (15)	0.9	(0.3–2.3)	0.775
Other CVID-associated conditions	143 (13.1)	6 (13.3)	26 (15)	0.9	(0.3–2.3)	0.775
Chronic lung disease	257 (16.4)	7 (15.6)	53 (30.6)	0.4	(0.2–1.0)	0.049
Interstitial lung disease	58 (5.3)	3 (6.7)	32 (18.5)	0.3	(0.1–1.1)	0.066
Bronchiectasis	148 (13.6)	4 (8.9)	33 (19.1)	0.4	(0.1–1.2)	0.114
Gastrointestinal disease	20 (1.8)	2 (4.4)	5 (2.9)	1.6	(0.3–8.3)	0.601
Enteropathy	7 (0.6)	1	3 (1.7)	1.3	(0.1–12.7)	0.828
IBD	13 (1.2)	1	2 (1.2)	1.9	(0.2–21.9)	0.591
Hepatic disease ^e	17 (1.6)	1	9 (5.2)	0.4	(0.1–3.4)	0.409
Granulomatous disease	11 (1.0)	0	7 (4.0)	n/a	n/a	n/a
Leukemia	7 (0.6)	0	0	n/a	n/a	n/a

CVID Cohort all patients included in the study, +Lymphoma CVID patients with lymphoma, +LPD –Lymphoma CVID patients with lymphoproliferative disease, but not lymphoma, OR odds ratio, CI confidence interval, NOS not otherwise specified, IBD inflammatory bowel disease, n/a p value cannot be calculated with at least one of the values being zero

^aDiagnoses are presented as reported by contributors to the USIDNET registry

^bDiagnoses include immune thrombocytopenia alone, autoimmune hemolytic anemia alone, and Evans syndrome; there were no patients with autoimmune neutropenia

^cDiagnoses include rheumatoid arthritis, systemic lupus erythematosus, vasculitis, and others including mixed connective tissue disease, spondyloarthropathies, juvenile arthritis, dermatomyositis, and inflammatory polyarthropathies

^dDiagnoses include psoriasis, vitiligo, lichen planus, alopecia areata, autoimmune enteritis or celiac disease, autoimmune hepatitis, type 1 diabetes mellitus, thyroiditis, uveitis, and iritis

^eDiagnoses include nodular regenerative hyperplasia of the liver, autoimmune hepatitis, granulomatous hepatitis, hepatomegaly, and liver function abnormalities

* p value was determined using chi-square calculation (categorical variables) and Student's t test (continuous variables)

Patients with lymphoproliferative disease had a significantly higher reported frequency of chronic lung disease than patients with lymphoma (p = 0.049)

Table 4

Frequency of gene mutations identified in 50 of 1091 CVID patients in the USIDNET registry^a

Gene	Total (N = 50)	+Lymphoma (N = 2)	+LPD –Lymphoma (N = 13)
TNFRSF13B (TACI)	27	2	8
NFKB2	5	0	1
CD19	3	0	0
TNFRSF12 (TWEAK)	2	0	0
PIK3CD	2	0	1
NFKB1	1	0	1
CR2 (CD21)	1	0	0
ICOS	1	0	0
TLR9	1	0	0
IRF2BP2	1	0	0
CD86	1	0	0
HLA-DQ	1	0	0
CTLA4	1	0	1
F5 (factor V Leiden)	1	0	0
SMC3	1	0	1
IFT140	1	0	0

Total all CVID patients included in the study that were found to have a genetic mutation, +Lymphoma CVID patients with lymphoma, +LPD –Lymphoma CVID patients with lymphoproliferative disease, but not lymphoma, TACI/transmembrane activator and calcium-modulating cyclophilin ligand, TWEAK cytokine tumor necrosis factor-like weak inducer of apoptosis, CD21 human complement receptor type 2

^aGene mutations are presented as reported by contributors to the USIDNET registry