Genes associated with common variable immunodeficiency: one diagnosis to rule them all?

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ABSTRACT

Common variable immunodeficiency (CVID) is a primary antibody deficiency characterised by hypogammaglobulinaemia, impaired production of specific antibodies after immunisation and increased susceptibility to infections. CVID shows a considerable phenotypical and genetic heterogeneity. In contrast to many other primary immunodeficiencies, monogenic forms count for only 2–10% of patients with CVID. Genes that have been implicated in monogenic CVID include *ICOS*, *TNFRSF13B* (TACI), *TNFRSF13C* (BAFF-R), *TNFSF12* (TWEAK), *CD19*, *CD81*, *CR2* (CD21), *MS4A1* (CD20), *TNFRSF7* (CD27), *IL21*, *IL21R*, *LRBA*, *CTLA4*, *PRKCD*, *PLCG2*, *NFKB1*, *NFKB2*, *PIK3CD*, *PIK3R1*, *VAV1*, *RAC2*, *BLK*, *IKZF1* (IKAROS) and *IRF2BP2*. With the increasing number of disease genes identified in CVID, it has become clear that CVID is an umbrella diagnosis and that many of these genetic defects cause distinct disease entities. Moreover, there is accumulating evidence that at least a subgroup of patients with CVID has a complex rather than a monogenic inheritance. This review aims to discuss current knowledge regarding the molecular genetic basis of CVID with an emphasis on the relationship with the clinical and immunological phenotype.

INTRODUCTION

Common variable immunodeficiency (CVID) is one of the most prevalent primary immunodeficiencies (PIDs) with an important morbidity and high number of medical encounters.[1 2] According to the international consensus statement, CVID is defined by a marked decrease in serum IgG, decreased IgM and/or IgA, poor antibody responses to vaccines, and exclusion of defined causes of hypogammaglobulinaemia.[2] Its prevalence is estimated between 1/10 000 and 1/50 000 in Caucasians; it is rarely described in Asian and African populations.[2 3] Age of onset is variable, with a peak incidence in childhood and in the second and third decades of life.[2 3] Although patients with CVID share many clinical and immunological features, the degree and severity of the presenting phenotype varies considerably between affected individuals.[2] The most consistent clinical feature is increased susceptibility to (respiratory tract) infections. Patients may also develop complications related to disrupted immune homoeostasis such as autoimmunity.[2] Besides impaired Ig production by B cells, abnormalities in almost all components of the immune system have been described in CVID.[2]

The majority of CVID cases occur sporadically.[2] About 5–25% of patients have a positive family history, of which most demonstrate an autosomal dominant inheritance.[2] So far, a monogenic cause has been identified in 2–10% of patients with CVID.[2 4] The majority of these genetic subtypes are very rare (figure 1 and table 1). The first CVID disease genes were discovered using a candidate gene approach based on single-gene knockout mice.[5–8] This might explain why many genetic defects described thus far are autosomal recessive. The past 4 years, next-generation sequencing (NGS) technologies have accelerated the discovery of both autosomal recessive and dominant CVID disease genes. In addition, it has become clear that the clinical diagnosis of CVID is an umbrella covering several genetic subtypes. In fact, many genes initially reported as CVID disease genes are now considered to be responsible for distinct disease entities (table 1). Moreover, it has been recently suggested that, apart from rare monogenic forms, CVID is a complex rather than a Mendelian disease.[2 4 9]

This review outlines current knowledge on the molecular basis of CVID, covering both monogenic and complex forms, and linking with clinical and immunological phenotypes.

GENES ASSOCIATED WITH MONOGENIC FORMS OF CVID

Genes encoding receptors and ligands

ICOS deficiency

Inducible T cell costimulator (ICOS) is a T cell surface receptor that belongs to the CD28/CTLA-4 (cytotoxic T lymphocyte-associated antigen 4) family (figure 2).[5] Reciprocal ICOS–ICOS ligand interactions are essential for germinal centre (GC) formation and terminal B cell differentiation, effector T cell responses and immune tolerance.[5]

ICOS was the first disease gene identified for monogenic forms of CVID, using a candidate gene approach based on prior evidence from single-gene knockout mice.[5] Hitherto, biallelic *ICOS* mutations resulting in complete loss of protein expression have been reported in seven families.[5 10–13] Haplotype analysis in the four German/Austrian families segregating an identical *ICOS* mutation was indicative for a common founder.[10 14]

ICOS-deficient patients had a variable phenotype with variable age of onset and severity (table 1).[5 10–13] Patients commonly presented recurrent respiratory tract infections and autoimmune complications.[5 10–13] Patients with two novel *ICOS* mutations published in 2015 extended the clinical spectrum: early onset inflammatory bowel disease, hepatomegaly with raised liver enzymes, *cytomegalovirus* viraemia and *Pneumocystis jirovecii* pneumonia.[12 13] Enteropathy in one ICOS-deficient

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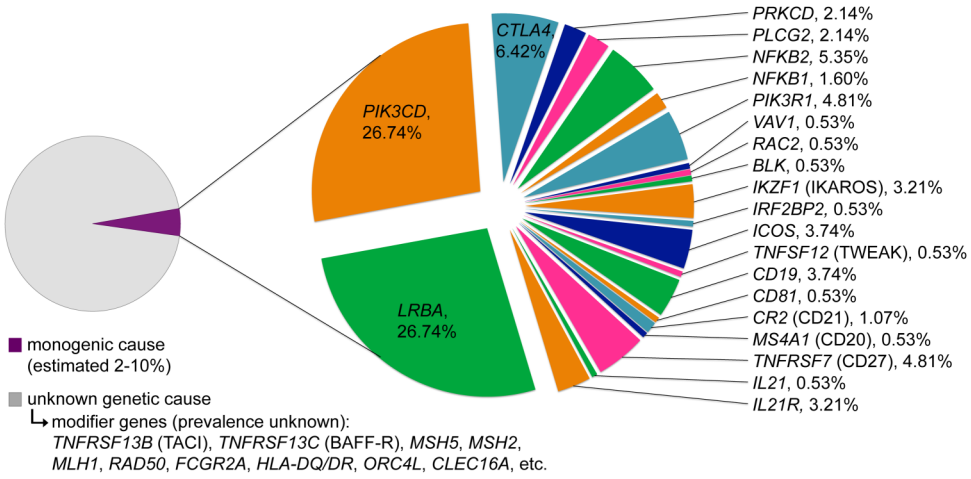

Figure 1 Estimated share of each disease gene within the common variable immunodeficiency population based on published cases.

patient resolved after haematopoietic stem cell transplantation while diarrhoea persisted in his non-transplanted sister. This indicates that inflammatory gut complications are disease-intrinsic.[12] Noteworthy, decreased ICOS expression was previously reported in an adult Caucasian man with Crohn's-like colitis and panhypogammaglobulinaemia.[15] Unfortunately, no mutation analysis of *ICOS* was performed.[15]

All ICOS-deficient patients had very low to absent memory B cells and some also showed a loss of bone marrow plasma cells.[5 10–14] This might be due to defective GC reactions in the absence of ICOS signalling.[14] ICOS-deficient patients also demonstrated varying degrees of T cell defects (table 1). In contrast to the first-reported German/Austrian families, the Japanese, Kuwaiti and Pakistani sibling pairs demonstrated pronounced T cell defects with viral and opportunistic infections resembling combined immunodeficiency (CID) rather than CVID.[5 10–14] Therefore, *ICOS* mutations are no longer considered to cause a pure CVID phenotype but result in a separate disease entity (ICOS deficiency).[12 13]

TACI and BAFF-R

Transmembrane activator and calcium modulator and cyclophilin ligand interactor (TACI, encoded by *TNFRSF13B*), B cell activating factor belonging to the tumour necrosis factor (TNF) family (BAFF)-receptor (BAFF-R, encoded by *TNFRSF13C*) and B cell maturation antigen (BCMA) are members of the TNF receptor superfamily (TNFRSF) important in peripheral B cell homoeostasis.[16] These receptors engage two ligands: BAFF and a proliferation inducing ligand (APRIL) (figure 2). Both ligand and receptor oligomerisation are necessary for optimal downstream signalling.[16] The TACI/BAFF-R/BCMA/BAFF/APRIL system signals through many pathways,[16 17] of which a selection is depicted in figure 2. How the TACI/BAFF-R/BCMA/BAFF/APRIL system fine-tunes B cell homoeostasis and the degree of mutual redundancy remain incompletely understood.[16 17] TACI mediates IgA and IgG class switch recombination (CSR), differentiation and survival of plasma cells, and T-independent responses to polysaccharide antigens. TACI also acts as an immunoregulator involved in central B cell tolerance and inhibiting peripheral B cell expansion.[16 17] BAFF–BAFF-R signalling promotes peripheral B cell survival and maturation in synergy with B cell receptor (BCR) signalling.[16] BCMA plays a role in long-term plasma cell survival in bone marrow.[16]

Variants in the genes encoding TACI and BAFF-R have been identified in patients with CVID by means of a candidate gene approach based on single-gene knockout mice.[6–8] Although initially thought to be fully penetrant, it is currently believed that monoallelic *TNFRSF13B* and monoallelic and biallelic *TNFRSF13C* variants are by themselves not sufficient to cause a CVID phenotype.[18–22]

TNFRSF13B (encoding TACI) variants

Biallelic and monoallelic loss-of-function variants in *TNFRSF13B* have been registered in at least 2147 patients based on the Jeffrey Modell Centers Global Network report.[1] Biallelic *TNFRSF13B* variants have always been associated with some degree of antibody deficiency,[6 7 19 20 23–27] except for a homozygous C104R variant in a 25-year-old member of a CVID-affected family who was asymptomatic and had normal Ig levels at the time of the study.[24] The latter individual could still have developed antibody deficiency later in life, however.[24] In contrast, monoallelic *TNFRSF13B* variants have also been detected in asymptomatic relatives and in 1–2% of the general population.[18–21 24 27]

A large variety of variants, mostly missense and nonsense variants, located in all domains of the TACI protein have been reported.[6 7 18–21 23–29] The monoallelic missense variants C104R and A181E account for 80% of all *TNFRSF13B* variants in patients with CVID.[6 7 18–21 23–29] In our cohort, we identified the C104R variant in a mother and daughter with CVID (unpublished data). The majority of *TNFRSF13B* variants do not or only slightly reduce TACI protein expression.[29] In particular, C104R interferes with ligand binding and A181E affects receptor oligomerisation.[29] Some patients with CVID have variants located in a highly conserved cytoplasmic domain of TACI (eg, S231R).[28] In these patients, recruitment of MyD88 to the cytoplasmic TACI domain was disrupted, causing impaired CSR and IgG production (figure 2).[28] Rarely, patients with CVID with truncating *TNFRSF13B* variants have been reported.[26]

Patients with CVID with monoallelic or biallelic *TNFRSF13B* variants can present with a variable phenotype encompassing the complete CVID clinical spectrum (table 1).[6 7 18–21] In some CVID-affected families, the same *TNFRSF13B* genotype has also been found in relatives with selective IgA deficiency (sIgAD) or IgG subclass deficiency.[6 7 20 27] Asymptomatic relatives carrying monoallelic *TNFRSF13B* variants have been shown to have in vitro functional B cell defects.[21]

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Table 1 Genes associated with monogenic forms of CVID: summary of genetic, clinical and immunological features

Gene, OMIM number	Number of publ. patients	Effect on protein	Inheritance	Onset	Clinical spectrum	Immunological spectrum	CVID or separate entity	Ref
Genes encoding receptors and ligands								
ICOS, *604558	15 (7 fam.)	LOF (absent expr.)	AR	Infancy to adulthood	RTI, GI infections, opportunistic infections, bacterial skin infections, localised herpes simplex infections, neuroborreliosis, bronchiectasis, AI (incl. AI cytopenia, rheumatic disease, IBD), BLH, splenomegaly, hepatomegaly, granulomata, malignancy.	↓ IgG, ↓ or nl IgM, ↓ or nl IgA, ↓ antibody responses to protein and/or polysaccharide vaccines, ↓ or nl total B cells, ↓↓ or absent memory B cells, absent bone marrow plasma cells, nl total/CD4$^+$/CD8$^+$ T cells, ↓ or nl CD4$^+$ and CD8$^+$ memory T cells, nl Treg cells, ↓ or nl circulating Tfh cells, ↓ or nl production of Th1/Th2/Th17 cytokines, ↓ CTLA-4 expr, nl CD40(L) expr.	ICOS deficiency	5 10–14
TNFRSF13B (TACI), *604907	2147	LOF (usually nl expr.)	Monoallelic/biallelic	Early childhood to adulthood	RTI, GI infections, bronchiectasis, AI (incl. AI cytopenia, rheumatic disease, IBD), BLH, splenomegaly (± splenectomy), granulomata, malignancy. Note: variants also found in asymptomatic individuals and in patients with sIgAD or IgG subclass deficiency.	↓ IgG, ↓ or nl IgM, ↓ or nl IgA, ↓ antibody responses to polysaccharide vaccines, ↓ or nl or ↑ total B cells, ↓ or nl memory B cells, ↓ or nl total/CD4$^+$/ CD8$^+$ T cells, ↓ or nl CD4$^+$ and CD8$^+$ naive/memory T cells, ↓ or nl Treg cells.	CVID, disease-predisposing	6 7 18–21 23–30
TNFRSF13C (BAFF-R), *606269	>80	LOF/GOF (usually nl expr.)	Monoallelic/biallelic	Infancy to late adulthood	RTI, GI infections, cholangitis, sacroiliitis, bronchiectasis, AI (incl. AI cytopenia, IBD), BLH, splenomegaly, granulomata, chronic diarrhoea with weight loss, failure to thrive. Note: variants also found in asymptomatic individuals and in patients with sIgAD or isolated IgM deficiency.	↓ IgG, nl to undetectable IgM, nl to undetectable IgA, ↓ antibody responses to polysaccharide vaccines, nl to absent total B cells, nl or ↑ transitional B cells, nl or ↓ memory B cells, nl total T cells, nl T cell subsets.	CVID, disease-predisposing	8 22 25 31–35†
TNFSF12 (TWEAK), *602695	3 (1 fam.)	LOF (nl expr.)	AD	Infancy	RTI, pneumococcal meningitis, osteomyelitis, AI thrombocytopenia and neutropenia, warts.	↓ IgG or low nl IgG with ↓↓ IgG2, ↓ IgM, ↓ IgA, ↓ antibody responses to protein and polysaccharide vaccines, ↓ or nl total B cells, ↓ memory B cells, ↑ naive B cells, nl or ↑ total T cells, nl total CD4$^+$ T cells, ↑ total CD8$^+$ T cells, ↑ double negative T cells, ↓↓ in vitro apoptotic function.	CVID	37
CD19, *107265	10 (7 fam.)	LOF (↓ or absent expr.)	AR	Infancy to early childhood	RTI, GI infections, bacterial conjunctivitis (± dacryocystitis), bacterial skin infections, bronchiectasis, intermittent microscopic haematuria, postinfectious glomerulonephritis, IgA nephropathy.	↓ IgG, ↓ or nl IgM, ↓ or nl IgA, ↓ antibody responses to protein and polysaccharide vaccines, nl total CD20$^+$ B cells, ↓↓ memory B cells, ↓↓ BCR signalling, nl CD81 expr., ↓ CD21 expr., nl total T cells, nl T cell subsets.	CVID	38 41–46
CD81, *186845	1	LOF (absent expr.)	AR	Infancy	RTI, AI thrombocytopenia, severe glomerulonephritis with progression to end-stage renal disease, undefined systemic inflammatory syndrome.	↓ IgG, nl IgM, ↓ to low nl IgA, ↓ antibody responses to protein and polysaccharide vaccines, nl total CD20$^+$ B cells, ↓↓ memory B cells, ↓↓ BCR signalling, absent CD19 expr., ↓ CD21 expr., nl total T cells, nl T cell subsets.	CVID	39
CR2 (CD21), *120650	2 (2 fam.)	LOF (absent expr.)	AR	Early childhood to childhood	RTI, chronic diarrhoea with weight loss, splenomegaly, myalgia, rigidity.	↓ IgG, ↓ or nl IgM, ↓ IgA, ↓ antibody response to polysaccharide vaccines, nl total CD19$^+$ B cells, ↓ memory B cells, mildly ↓ BCR signalling, nl CD19/CD81 expr., nl total T cells, nl T cell subsets.	CVID	40 49
MS4A1 (CD20), *112210	1	LOF (absent expr.)	AR	Infancy	RTI	↓ IgG, nl IgM, nl IgA, ↓ antibody responses to polysaccharide vaccines, nl total B cells, ↓↓ memory B cells, nl total T cells, nl T cell subsets.	CVID	50
TNFRSF7 (CD27), *186711	17 (9 fam.)	LOF (↓ or absent expr.)	AR	Infancy to childhood	Chronic EBV viraemia, severe/atypical EBV-associated infections (eg, severe mononucleosis, pneumonia, meningitis/encephalitis, oral/perianal ulcers, uveitis),	↓ or nl or ↑ IgG, ↓ or nl IgM, ↓ or nl IgA, ↓ or nl antibody responses to protein and/or polysaccharide vaccines, ↓ or nl total B cells, absent memory B	CD27 deficiency	51–53

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Table 1 Continued

Gene, OMIM number	Number of publ. patients	Effect on protein	Inheritance	Onset	Clinical spectrum	Immunological spectrum	CVID or separate entity	Ref
					EBV-induced lymphoproliferation (eg, BLH, splenomegaly, hepatomegaly, lymphocytic infiltration of non-lymphoid organs, HLH, lymphoma), RTI, bronchiectasis, bacterial skin infections, giardiasis, fulminant bacterial sepsis.	cells, nl or ↑ transitional B cells, nl or ↑ CD21^{low} B cells, ↓ or nl CD4^{+} T cells, nl or ↑ CD8^{+} T cells, ↓ or nl CD8^{+} memory T cells, ↓ or nl in vitro T cell proliferation responses, ↓ or nl or ↑ NK cells, ↓ or nl NK cell cytotoxicity, ↓ or nl iNKT cells.		
IL21, *605384	1	LOF (nl expr.)	AR	Infancy	RTI, early onset IBD, failure to thrive, recurrent oral aphthous ulcers.	↓ IgG, nl IgM, nl IgA, ↑ IgE, ↓ antibody responses to protein and polysaccharide vaccines, ↓ total B cells, ↓↓ memory B cells, ↓ naive B cells, ↑ transitional B cells, nl total/CD4^{+}/CD8^{+} T cells, ↓ in vitro T cell proliferation responses.	IL-21 deficiency	55
IL21R, *605383	8 (6 fam.)	LOF (↓ or absent expr.)	AR	Infancy to early childhood	RTI, GI infections, opportunistic infections (including cryptosporidiosis with progression to end-stage biliary/liver disease), pulmonary tuberculosis, bronchiectasis, BLH, hepatosplenomegaly, discoid lupus/chronic inflammatory skin disease, failure to thrive.	↓ or nl IgG, nl or ↑ IgM, ↓ or nl IgA, nl or ↑ IgE, ↓ antibody responses to protein and/or polysaccharide vaccines, ↓ or nl or ↑ total B cells, ↓ or nl memory B cells, nl or ↑ transitional B cells, nl total T cells, ↓ or nl CD4^{+} T cells, ↓ or nl CD8^{+} T cells, ↓ or nl Tfh cells, ↓ or nl in vitro B and T cell proliferation responses, ↓ or nl production of Th cytokines, ↓ or nl NK cells, ↓ or nl NK cell cytotoxicity.	IL-21R deficiency	54 56–58
LRBA, *606453	>50	LOF (majority ↓ or absent expr.)	AR	Infancy to childhood	Severe AI (incl. AI cytopenia, severe IBD, type 1 diabetes mellitus), severe (EBV-induced) lymphoproliferation with generalised BLH and lymphocytic infiltration of organs (eg, kidney, brain), LIP, GLILD, granulomata, chronic lung disease, bronchiectasis, splenomegaly, hepatomegaly, malignancy, finger clubbing, failure to thrive, RTI, GI infections, opportunistic infections, bacterial skin infections, deep abscesses, bacterial conjunctivitis, warts, mollusca contagiosa, food allergy, allergic dermatitis, urticaria, growth hormone deficiency.	↓ or nl or ↑ IgG, ↓ or nl IgM, ↓ or nl or ↑ IgA, ↓ or nl antibody responses to protein and/or polysaccharide vaccines, ↓ or nl total B cells, ↓ or nl memory B cells, ↓ or nl plasmablasts, ↓ or nl or ↑ transitional B cells, ↓ or nl or ↑ naive B cells, nl or ↑ CD21^{low} B cells, ↓ B cell proliferation and Ig secretion, ↓ or nl total lymphocytes, ↓ or nl or ↑ total/CD4^{+}/CD8^{+} T cells, nl or ↑ CD4^{+}/CD8^{+} memory T cells, ↓ or nl CD4^{+}/CD8^{+} naive T cells, ↓ or nl Treg cells, nl or ↑ double negative T cells, nl or ↑ Tfh cells, ↓ or nl in vitro T cell proliferation responses, ↓ or nl Fas-mediated apoptosis, ↓ CTLA-4 surface expr., ↑ sCD25, ↓ or nl NK cells, ↓ or nl neutrophils.	LRBA deficiency	59 62–72
CTLA4, *123890	23 (12 fam.)	LOF (usually ↓ expr.)	AD	Infancy to adulthood	Severe AI (incl. AI cytopenia, severe IBD, type 1 diabetes mellitus), severe (EBV-induced) lymphoproliferation with generalised BLH and lymphocytic infiltration of organs (eg, kidney, brain, bone marrow), GLILD, granulomata, bronchiectasis, splenomegaly, hepatomegaly, malignancy, failure to thrive, RTI, GI infections, opportunistic infections, pulmonary tuberculosis, warts, food allergy, allergic dermatitis. Note: variants also found in asymptomatic individuals.	↓ or nl IgG, ↓ or nl IgM, ↓ or nl IgA, ↓ or nl antibody responses to polysaccharide vaccines, ↓ or nl total B cells, ↓ or nl memory B cells, nl or ↑ CD21^{low} B cells, ↓ or nl total lymphocytes, ↓ or nl total T cells, ↓ or nl CD4^{+}/CD8^{+} T cells, ↓ or nl CD4^{+}/CD8^{+} naive T cells, nl or ↑ double negative T cells, nl or ↑ Treg cells, ↓ FoxP3/CD25 expr. on Treg cells, ↓ suppressive activity Treg cells, ↑ activity effector T cells, ↓ or nl NK cells, ↓ or nl NKT cells.	CTLA-4 deficiency	60 61 73 74
Genes encoding intracellular signalling molecules								
PRKCD, *176977	6 (4 fam.)	LOF (↓ or absent expr.)	AR	Infancy to early childhood	Severe systemic AI with features reminiscent of systemic lupus erythematosus, severe (EBV/CMV-induced) lymphoproliferation with generalised BLH, splenomegaly, hepatomegaly, RTI, GI infections, urinary tract infections, failure to thrive.	↓ or nl IgG, nl or ↑ IgM, nl or ↑ IgA, ↓ or nl antibody responses to protein and/or polysaccharide vaccines, ↓ or nl or ↑ total B cells, ↓ memory B cells, nl or ↑ transitional B cells, nl or ↑ naive B cells, ↑ CD21^{low} B cells, ↓ or nl total/CD4^{+}/CD8^{+} T	PKCδ deficiency	75 80–82

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Table 1 Continued

Gene, OMIM number	Number of publ. patients	Effect on protein	Inheritance	Onset	Clinical spectrum	Immunological spectrum	CVID or separate entity	Ref
						cells, nl or ↑ double negative T cells, mildly ↓ or nl in vitro T cell proliferation responses, ↓ or nl NK cells, ↓ or nl NK cell cytotoxicity, nl NKT cells, ↓ or nl neutrophil microbial killing capacity.		
PLCG2, *600220	30 (4 fam.)	GOF (usually nl expr.)	AD	Infancy to childhood	Cold urticaria (negative ice cube skin test, positive evaporative cooling skin test), atopy (food, airway, skin), skin granulomata, blistering skin lesions, RTI, onychomycosis, varicella zoster infections, bacterial skin infections, AI (mainly involving skin and thyroid gland).	↓ or nl IgG, ↓ or nl IgM, ↓ or nl IgA, nl or ↑ IgE, ↓ or nl antibody responses to polysaccharide vaccines, nl total B cells, ↓ or nl memory B cells, ↓ BCR signalling, ↓ in vitro B cell proliferation responses, negative cold agglutinins and cryoglobulins, positive antinuclear antibodies, nl total T cells, nl T cell subsets, ↓ or nl NK cells, ↓ or nl NKT cells.	PLAID	83 84
NFKB2, *164012	17 (10 fam.)	LOF (↓ or nl expr.)	AD	Infancy to childhood	RTI, GI infections, localised herpes simplex infections, onychomycosis, bronchiectasis, pituitary hormone deficiencies (mainly ACTH deficiency), AI (mainly involving skin, hair and nails).	↓ or nl IgG, ↓ or nl IgM, ↓ or nl IgA, ↓ or nl antibody responses to protein and/or polysaccharide vaccines, absent or ↓ or nl B cells, ↓ or nl memory B cells, nl or ↑ total T cells, nl $CD4^+/CD8^+$ T cells, ↓ or nl $CD4^+/CD8^+$ memory T cells, nl or ↑ recent thymic emigrant $CD4^+$ T cells, ↓ or nl Tfh cells, ↓ or nl Treg cells, ↓ or nl in vitro T cell proliferation responses, ↓ or nl NK cells, ↓ or nl NK cell cytotoxicity.	NF-κB2 deficiency	85 87–91
NFKB1, *164011	18 (3 fam.)	LOF (↓ expr.)	AD	Early childhood to adulthood	RTI, GI infections, bacterial skin infections, AI (mainly involving blood cells, gut, hair and thyroid gland), pyoderma gangrenosum, bronchiectasis, chronic lung disease, LIP, BLH, splenomegaly, hepatomegaly, malignancy. Note: variants also found in asymptomatic individuals and in patients with other antibody deficiencies (eg, IgG subclass deficiency).	Full immunological phenotype not reported. ↓ or nl IgG, ↓ or nl IgM, ↓ or nl IgA, ↓ or nl antibody responses to protein and/or polysaccharide vaccines, nl total B cells, nl total T cells.	NF-κB1 deficiency	86
PIK3CD, *602839	> 50	GOF (usually nl expr.)	AD	Infancy to early childhood	RTI, GI infections, bacterial skin infections, deep abscesses, warts, persistent CMV/EBV viraemia, failure to thrive, bronchiectasis, AI (AI cytopenia, IBD, AI primary sclerosing cholangitis), (EBV/CMV-induced) lymphoproliferation with (generalised) BLH, splenomegaly, hepatomegaly, malignancy (mainly lymphoma).	↓ or nl or ↑ IgG, ↓ or nl IgG2, ↓ or nl IgA, ↓ or nl or ↑ IgM, ↓ or nl antibody responses to protein and/or polysaccharide vaccines, ↓ or nl total B cells, absent or ↓ or nl memory B cells, nl or ↑ transitional B cells, ↓ or nl naive B cells, ↓ or nl total lymphocytes, ↓ or nl total/$CD4^+/CD8^+$ T cells, nl or ↑ $CD4^+/CD8^+$ memory T cells, ↓ or nl $CD4^+/CD8^+$ naive T cells, nl Treg cells, ↑ T cell activation-induced cell death, ↓ or nl or ↑ NK cells, ↓ or nl or ↑ NKT cells, ↓ or nl NK cell cytotoxicity.	APDS	76 77 92–97
PIK3R1, *171833	12 (9 fam.)	LOF (nl expr.)	AD	Infancy to childhood	RTI, GI infections, bacterial conjunctivitis, persistent CMV/EBV viraemia, failure to thrive, bronchiectasis, AI (AI cytopenia, IBD, rheumatic disease), (EBV/CMV-induced) lymphoproliferation with (generalised) BLH, splenomegaly (± splenectomy), hepatomegaly, malignancy (mainly lymphoma).	Full immunological phenotype not reported in ref 100. ↓ or nl IgG, ↓ or nl or ↑ IgM, ↓ IgA, ↓ antibody responses to polysaccharide vaccines, ↓ or nl total B cells, ↓ or nl memory B cells, nl or ↑ transitional B cells, nl or ↑ total T cells, ↓ or nl $CD4^+$ (total/naive/memory) T cells, ↓ or nl or ↑ $CD8^+$ (total/naive/memory) T cells, nl or ↑ Treg cells, nl double negative T cells, ↓ Th17 cells, ↓ or nl NK cells.	APDS-like	98–101

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Table 1 Continued

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VAV1, *164875	1	LOF (↓ expr.)	AD	Adulthood	Full clinical phenotype not reported. RTI, GI infections, genitourinary infections, bronchiectasis.	Full immunological phenotype not reported. ↓ IgG, absent IgM/IgA, nl total B cells, nl total T cells, ↓ $CD4^+$ T cells, nl $CD8^+$ T cells, ↓ in vitro T cell proliferation responses to mitogens.	Vav1 deficiency	103
RAC2, *602049	2 (1 fam.)	LOF (absent expr.)	AR	Infancy to childhood	RTI, failure to thrive, bronchiectasis, arthralgia, AI endocrinopathy, BLH, poststreptococcal glomerulonephritis (±progression to end-stage renal disease), solar urticaria, food allergy, coagulopathy.	↓ IgG, ↓ IgM, ↓ IgA, ↓ antibody responses to polysaccharide vaccines, ↓↓ total B cells, nl total/ $CD4^+$/$CD8^+$ T cells, ↓ $CD4^+$ and $CD8^+$ naive T cells, ↓ recent thymic emigrant $CD4^+$ T cells, ↓ Treg cells, ↓ TRECs, ↓ KRECs, nl neutrophils, ↓ neutrophil chemotaxis, ↓ and aberrant morphology of neutrophil granules.	RAC2 deficiency	104
BLK, *191305	2 (1 fam.)	LOF (nl expr.)	AD	Infancy	RTI, bacterial skin infections.	↓ IgG, ↓ or nl IgA, ↓ or nl IgM, ↓ antibody responses to polysaccharide vaccines, ↓ or nl total B cells, nl total T cells.	CVID	105
IKZF1, *603023	21 (6 fam.)	LOF (↓ or nl expr.)	AD	Early childhood to late adulthood	RTI, *Streptococcus pneumoniae* infections, GI infections, bacterial skin infections, apthous ulcers, AI (AI cytopenia), malignancy (acute lymphoblastic leukaemia). Note: variants also found in asymptomatic individuals.	↓ IgG, ↓ or nl IgM, ↓ or nl IgA, ↓ or nl antibody responses to protein and/or polysaccharide vaccines, ↓↓ or ↓ or nl total B cells, ↓ or nl memory B cells, nl or ↑ total T cells, ↓ or nl or ↑ $CD4^+$ T cells, nl or ↑ $CD8^+$ T cells, nl in vitro T cell proliferation responses, nl Fas-mediated apoptosis, ↓ or nl or ↑ NK cells.	CVID	78†
IRF2BP2, *615332	3 (1 fam.)	GOF (↑ expr.)	AD	Early childhood to childhood	RTI, AI (IBD, type 1 diabetes mellitus, psoriasis).	↓ IgG, ↓ IgG2, ↓ to undetectable IgM, undetectable IgA, ↓ antibody responses to protein and/or polysaccharide vaccines, nl total B cells, ↓↓ or ↓ memory B cells, nl total/$CD4^+$/$CD8^+$ T cells, ↓ or nl NK cells.	CVID	79

Disease onset: infancy (0–2 years), early childhood (3–8 years), childhood (9–17 years), adulthood (18–50 years), late adulthood (>50 years).
†Unpublished cases from our cohort.
↓, decreased; ↑, increased; ±, with or without; ACTH, adrenocorticotropic hormone; AD, autosomal dominant; AI, autoimmun(e)(ity); APDS, activated PI3 kinase δ syndrome; AR, autosomal recessive; BCR, B cell receptor; BLH, benign lymphoid hyperplasia; CMV, cytomegalovirus; CTLA-4, cytotoxic T lymphocyte-associated antigen 4; CVID, common variable immunodeficiency; EBV, Epstein–Barr virus; expr., expression; fam., families; GI, gastrointestinal; GLILD, granulomatous lymphocytic interstitial lung disease; GOF, gain-of-function; HLH, hemophagocytic lymphohistiocytosis; iNKT, invariant natural killer T; IBD, inflammatory bowel disease; ICOS, inducible T cell costimulator; KRECs, κ-deleting recombination excision circles; LRBA, lipopolysaccharide-responsive beige-like anchor protein; LIP, lymphoid interstitial pneumonia; LOF, loss-of-function; nl, normal; NFKB, nuclear factor of kappa light chain enhancer of activated B cells; OMIM, Online Mendelian Inheritance in Man; PKCδ, protein kinase C delta; PLAID, PLCγ2-associated antibody deficiency and immune dysregulation; PLCγ2, phospholipase C gamma 2; publ., published; ref: references; RTI, respiratory tract infections; sIgAD, selective IgA deficiency; TACI, transmembrane activator and calcium modulator and cyclophilin ligand interactor; Tfh, follicular helper T ($CD4^+CD45RO^+CXCR5^+$); Th, T helper ($CD4^+$); TRECs, T cell receptor excision circles; Treg, regulatory T ($CD4^+CD25^+FoxP3^+$).

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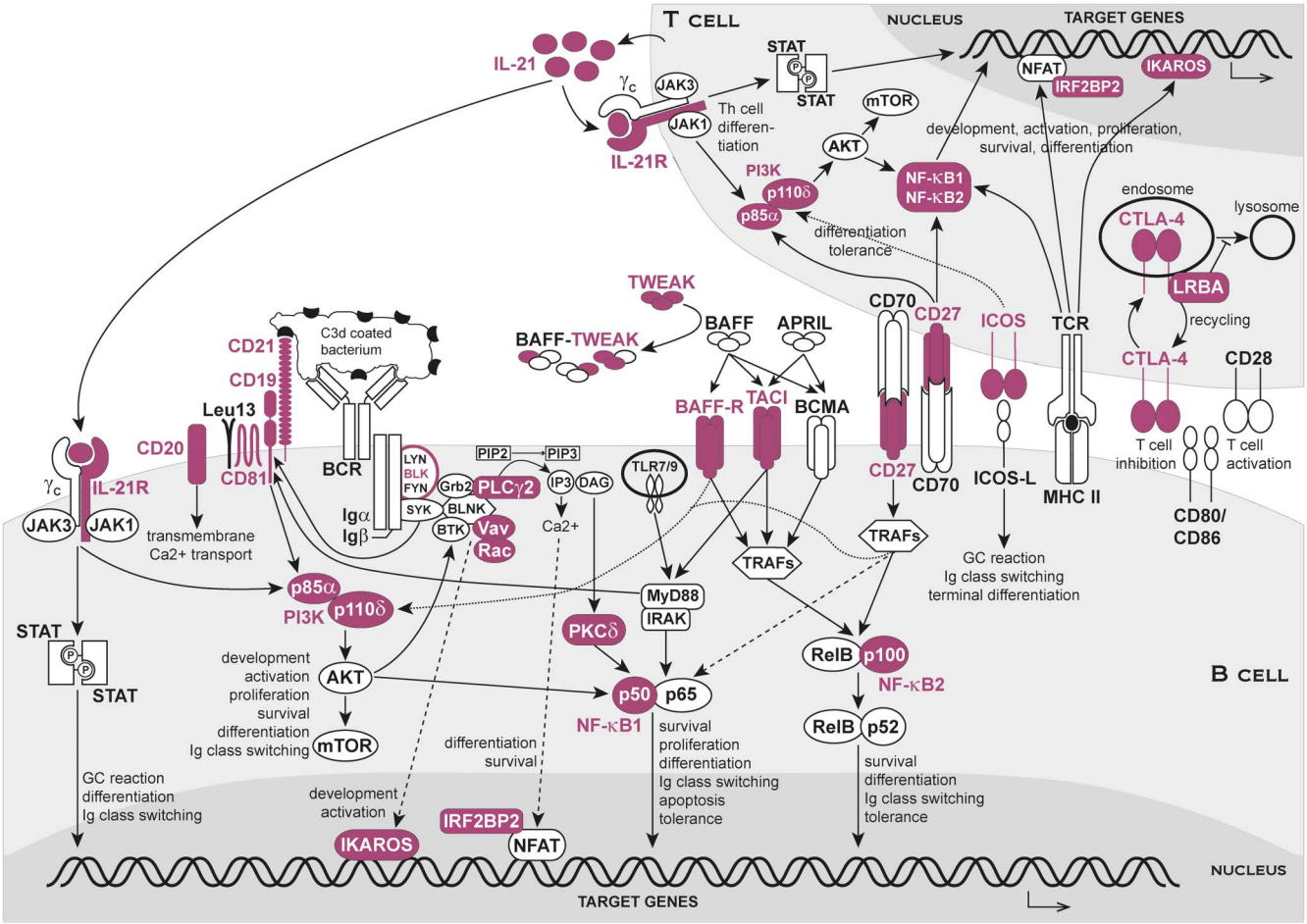

Figure 2 Scheme comprising proteins encoded by common variable immunodeficiency disease genes (purple). Only the most important interacting molecules, pathways and functions relevant to this review are depicted. See text for details.

Because of the high frequency of heterozygous *TNFRSF13B* variants in the general population, it is believed that these variants alone cannot explain the clinical phenotype in patients with CVID.[18–21] Still, heterozygous *TNFRSF13B* variants can increase the risk for developing CVID by compromising B cell function and may influence the final phenotype.[29 30] TACI cooperates synergistically with Toll-like receptors (TLRs) in driving B cell activation and Ig production (figure 2).[16] B cells in many patients with CVID show impaired TLR7 and TLR9 responses.[28] Loss-of-function *TNFRSF13B* variants might aggravate the effect of already impaired TLR signalling, or, alternatively might impose TLR signalling defects.[28] Furthermore, patients with CVID with heterozygous *TNFRSF13B* variants have a higher risk of developing autoantibody-mediated autoimmunity.[17 30] In our cohort, the daughter carrying a heterozygous C104R variant developed autoimmune cytopenias and psoriasis (unpublished data). In contrast, patients with biallelic *TNFRSF13B* variants seem to be protected from autoimmunity.[30]

TNFRSF13C (encoding BAFF-R) variants

Biallelic and monoallelic *TNFRSF13C* variants have been reported in about 80 patients with CVID.[8 22 25 31–35] More than 90% of reported cases were heterozygous or homozygous for the P21R missense variant.[22 25 31–35] In addition, other patients with CVID were found to be heterozygous for H159Y, compound heterozygous for P21R and H159Y, or compound heterozygous for P21R and a complex P21R/H159Y allele.[25 31 32] One patient with CVID had heterozygous P21R and H159Y variants *in cis*.[35] Interestingly, the father and sister of the last-mentioned patient also had these variants *in cis* but presented with isolated IgM deficiency, respectively, sIgAD.[35] Moreover, heterozygous and homozygous P21R variants and heterozygous H159Y variants have also been identified in asymptomatic relatives and healthy controls.[22 31] To our knowledge, biallelic variants that include H159Y and the heterozygous P21R/H159Y allele in *TNFRSF13C* have never been reported in asymptomatic individuals.[25 32 35]

The P21R variant reduces BAFF ligand binding (figure 2), suggestive for loss-of-function.[22] In contrast, the H159Y variant has been implicated in lymphoma development and was shown to increase tumor necrosis factor receptor-associated factor (TRAF) recruitment and downstream BAFF-R signalling (figure 2) when overexpressed in a HEK293 cell line, suggestive for gain-of-function.[36] Further studies will be necessary to determine the role of H159Y variants in CVID pathogenesis. The vast majority of patients with monoallelic or biallelic *TNFRSF13C* variants had normal BAFF-R protein expression.[22 31] Thus far, deficiency of BAFF-R protein expression was reported in four patients with CVID.[8 34 35] Two of those BAFF-R-deficient patients were a brother and sister sibship born from consanguineous parents with a homozygous *TNFRSF13C* 24-bp deletion causing complete loss of BAFF-R expression.[8] Furthermore, reduced (but not absent) BAFF-R expression was identified in one patient with CVID with a homozygous P21R

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variant and the above-mentioned patient with CVID with the heterozygous P21R/H159Y allele.[34 35] In our cohort, we identified a Caucasian male patient with CVID homozygous for P21R with absent BAFF-R expression. Additional analysis is ongoing (unpublished data).

Most reported patients with CVID with *TNFRSF13C* variants had adulthood-onset recurrent respiratory tract infections. Nonetheless, some patients already developed symptoms at a young age and/or additionally suffered from severe CVID-related complications (table 1).[8 22 25 31–35] Our unpublished patient presented with recurrent airway infections, chronic autoimmune thrombocytopenia and severe chronic diarrhoea at the age of 60 years. Laboratory findings varied between patients (table 1).[8 22 25 31–35] Curiously, the BAFF-R-deficient sib pair and our unpublished case had important B cell lymphopenia with a relative increase in transitional B cells, which seems contradictory with their late disease onset and/or relatively mild clinical phenotype.[8]

Analogous to *TNFRSF13B* (TACI) variants, the role of *TNFRSF13C* (BAFF-R) variants in CVID is controversial. It is currently believed that an abnormal BAFF-R function predisposes to but does not suffice for CVID development.[22]

TWEAK deficiency

One CVID pedigree with autosomal dominant inheritance had a mutation in *tumour necrosis factor superfamily member 12* (*TNFSF12*), encoding TNF-like weak inducer of apoptosis (TWEAK) (table 1).[37] TWEAK mainly exerts effects on endothelial and innate immune cells.[37] In addition to diminished TWEAK-induced signalling, mutant TWEAK associated with BAFF monomers thereby impeding BAFF-mediated signalling in B cells (figure 2).[37] More patients will need to be identified to determine if TWEAK deficiency should be considered as a form of CVID or as a separate disorder.

B cell co-receptor complex deficiency

The B cell co-receptor complex is composed of four cell-surface proteins: CD19, CD21 (complement receptor 2, CR2), CD81 and Leu13 (figure 2). It lowers the threshold for B cell activation upon antigen binding to the BCR.[38]

CD19, CD81 and CD21 deficiencies occur in autosomal recessive forms of CVID, and were identified by use of a candidate gene approach.[38–40]

CD19 and CD81 deficiencies

Biallelic *CD19* mutations resulting in absent CD19 surface expression have been reported in seven CVID-affected families.[38 41–46] In an additional patient with CVID, absent CD19 surface expression was due to a biallelic *CD81* splice site mutation.[39] Initially, this *CD81* mutation was assumed to completely abolish CD81 protein expression.[39] However, it was recently demonstrated that in fact a truncated CD81 protein was produced.[47] Both the mutant CD81 and the normal CD19 protein were retained intracellularly, resulting in absent CD81 and CD19 surface expression.[47]

All CD19-deficient patients and the CD81-deficient patient developed symptoms in early childhood and suffered from recurrent infections.[38 39 41–46] Only the CD81-deficient patient showed autoimmune and inflammatory complications (table 1).[39] This clinical discrepancy might be because CD81, in contrast to CD19, is involved in many immunological responses.[39] All CD19-deficient and CD81-deficient patients had normal total $CD20^+$ B cell numbers but reduced switched memory B cells.[38 39 41–46] Impaired BCR/co-receptor complex signalling in these patients resulted in defective somatic hypermutation and CSR, as well as poor terminal differentiation into memory B cells and plasma cells.[48]

Interestingly, a female patient with isolated IgG1 deficiency was also found to have absent CD19 expression due to a homozygous *CD19* mutation.[45] She had recurrent respiratory tract infections but mainly suffered from severe IgA nephropathy. In contrast to CD19-deficient patients with CVID, memory B cells and responses to protein vaccines were normal.[45] It is unclear why this CD19-deficient patient developed isolated IgG1 deficiency and not CVID.[45]

CD21 deficiency

Biallelic *CD21* mutations causing loss of CD21 protein expression have been published in two unrelated patients with CVID.[40 49] CD19 and CD81 expression were normal. Compared with CD19-deficient and CD81-deficient patients with CVID, CD21-deficient patients demonstrated a later age of onset, milder infections and less pronounced humoral immune defects (table 1).[40 49] Wentink *et al* provided evidence that CD21-deficient patients can still mount proper B cell responses against antigenic stimuli but with reduced memory formation, whereas CD19-deficient and CD81-deficient patients have a more profoundly disturbed B cell response.[49] On the other hand, CD21-deficient patients presented with chronic diarrhoea, splenomegaly and/or severe myalgia, which was not seen in CD19-deficient or CD81-deficient patients.[38–46 49]

CD20 deficiency

CD20 is part of a B cell surface complex involved in transmembrane Ca^{2+} transport, which is important in B cell signal transduction, proliferation and differentiation (figure 2).[50] Knowledge on the exact biology of CD20 is, however, limited. CD20 is encoded by *membrane-spanning 4A1* (*MS4A1*). Using a candidate gene approach, a homozygous *MS4A1* mutation resulting in complete lack of CD20 protein expression has been identified in a single patient born from consanguineous parents.[50] She did not completely fulfil diagnostic criteria for CVID as only serum IgG was decreased with normal IgM and IgA.[50] She presented with early onset recurrent respiratory tract infections, markedly reduced class-switched memory B cells and impaired antibody responses to polysaccharide vaccines (table 1).[50] CD20 deficiency may disrupt normal Ca^{2+} fluxing in B cells thereby compromising cell cycle progression and optimal B cell activation, which may explain the CVID-like phenotype.[50]

CD27 deficiency

CD27, a lymphocyte surface receptor encoded by *TNFRSF7*, interacts with CD70 and regulates survival, function and differentiation of T, B, natural killer (NK) and plasma cells (figure 2).[51] CD27 is also used as a marker of memory B cells, like in immunophenotypical classification of CVID.[52] A homozygous *TNFRSF7* mutation was first identified by targeted gene sequencing in a patient with absent CD27 protein expression.[51] So far, CD27 deficiency has been reported in 17 patients of whom 15 had homozygous *TNFRSF7* mutations (all from a consanguineous kindred) and one had a compound heterozygous *TNFRSF7* mutation.[51–53] Remarkably, in one CD27-deficient patient only a single *TNFRSF7* mutation was identified, even after extensive analysis of the entire gene locus.[52] The authors concluded that transcription of the second allele could be influenced by a mutation in a distant regulatory element or by other regulatory mechanisms.[52]

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The phenotype of CD27-deficient patients varied, even between those with the same genotype (table 1).[51–53] Importantly, almost all CD27-deficient patients suffered from severe and/or atypical Epstein–Barr virus-associated features (table 1).[51–53] Five patients died of disease-related complications.[52] Only three of all reported patients had primary hypogammaglobulinaemia initially diagnosed as CVID.[51–53] With more patients being reported, CD27 deficiency is currently considered as a lymphoproliferative syndrome distinct from CVID.[52]

IL-21 and IL-21R deficiencies

Interleukin 21 (IL-21) is predominantly produced by T cell subsets.[54] In contrast, IL-21 receptor (IL-21R) is widely expressed on lymphoid and myeloid cells and exerts pleiotropic immune functions.[54] Regarding humoral immunity, IL-21-IL-21R signalling is involved in GC formation, B cell differentiation and CSR, and follicular helper T cell development (figure 2).[54]

Biallelic loss-of-function mutations in *IL21* and *IL21R* were detected in consanguineous families using whole-exome sequencing (WES) combined with either homozygosity mapping or candidate gene sequencing.[55 56] To our knowledge, one patient with IL-21 deficiency and eight with IL-21R deficiency have been published.[54–58]

All IL-21(R)-deficient patients had a severe clinical presentation with high morbidity and mortality in childhood (table 1).[54–58] IL-21(R)-deficient patients typically suffered from respiratory tract infections, inflammatory complications and/or opportunistic infections like *Cryptosporidiosis* and *Pneumocystis jirovecii* pneumonia.[54–58] Some IL-21(R)-deficient patients showed an aberrant B cell phenotype with reduced switched memory B cells. In addition, some patients demonstrated functional defects in T and NK cells (table 1).[54–58]

Several IL-21(R)-deficient patients were initially diagnosed with CVID, before the onset of opportunistic infections.[55 57] However, over time it has become evident that IL-21 and IL-21R deficiencies represent forms of CID rather than CVID.[54–58]

LRBA and CTLA-4 deficiencies

Lipopolysaccharide-responsive beige-like anchor protein (LRBA) is a cytosolic protein localised in endoplasmatic reticulum, trans-Golgi apparatus, endocytosis vesicles and lysosomes.[59] It is expressed by almost all cell types with higher expression levels in immune effector cells.[59] LRBA functions in polarised vesicle trafficking and polarised responses of immune effector cells, autophagy, and positive regulation of cell survival.[59]

CTLA-4 is an inhibitory T cell receptor (TCR) that negatively regulates immune responses. CTLA-4 competes with the costimulatory protein CD28 for binding to CD80/CD86, thereby preventing excessive T cell activation and maintaining immune tolerance (figure 2).[60 61] It was recently demonstrated that LRBA plays a role in CTLA-4 surface expression.[62] LRBA is thought to rescue endosomal CTLA-4 from degradation via the lysosomal pathway and to facilitate its trafficking back to the cell surface upon TCR stimulation (figure 2).[62]

LRBA deficiency

Biallelic loss-of-function *LRBA* mutations were identified by three independent groups by using linkage analysis in multiple consanguineous families or by using WES with or without homozygosity mapping in single consanguineous families.[59 63 64] Hitherto, biallelic *LRBA* mutations resulted in reduced or absent protein expression in all cases except one.[59 62–72]

The clinical and immunological phenotype of LRBA-deficient patients is very variable (table 1).[59 62–72] The majority of reported LRBA-deficient patients was clinically diagnosed with CVID, some with autoimmune lymphoproliferative syndrome (ALPS)-like or immune dysregulation, polyendocrinopathy, enteropathy, X-linked-like disease.[59 62–72] A common denominator in all LRBA-deficient patients is early onset of severe autoimmunity. Other recurring clinical features are recurrent infections and severe lymphoproliferative disease with increased risk of lymphoma.[59 62–72] More than half of cases had varying degrees of hypogammaglobulinaemia and most patients had decreased switched memory B cells.[59 62–72] Importantly, LRBA deficiency is characterised by a progressive course and high mortality rate.[59 62–72] Although first identified in patients with CVID,[59] it is currently considered as an immune dysregulation syndrome separate from CVID.[62–72]

CTLA-4 deficiency

Heterozygous mutations in *CTLA4* were identified by two independent groups using either WES combined with linkage analysis in a large family or WES combined with candidate gene sequencing.[60 61] Most *CTLA4* mutations resulted in reduced CTLA-4 expression suggesting haploinsufficiency.[60 61 73 74] Other *CTLA4* mutations were predicted to interfere with ligand binding or protein stability, which might exert a dominant-negative effect.[61] Many CTLA-4-deficient patients were clinically diagnosed with CVID.[60 61 73 74] However, *CTLA4* mutations were also detected in family members who were asymptomatic or had sIgAD, pointing to incomplete penetrance.[60 61 73 74] Alternatively, the phenotype may be modulated by other disease-modifying genes and/or environmental influences. Of note, since age of onset is variable, young *CTLA4* mutation carriers who are currently asymptomatic may still develop disease later in life.[61]

Overall, the phenotype of CTLA-4 deficiency is reminiscent of that of LRBA deficiency: autoimmunity, recurrent infections, benign lymphoproliferation, and varying Ig levels and B cell and T cell defects (table 1).[60 61 73 74] Regulatory T (Treg) cells were normal in numbers but had a markedly reduced suppressive function.[60 61 73 74] Treg cells of asymptomatic *CTLA4* mutation carriers also had reduced suppressive activity although they did express higher levels of CTLA-4 compared with those of their symptomatic relatives.[60 61]

Analogous to LRBA deficiency, CTLA-4 deficiency was first described in patients with CVID but is currently considered as a new immune dysregulation syndrome.[60 61 73 74]

Genes encoding intracellular signalling molecules

Protein kinase C delta (PKCδ) is a key component in BCR-mediated signalling downstream of Bruton's tyrosine kinase, phospholipase C gamma 2 (PLCγ2), B-lymphoid tyrosine kinase (BLK), Vav guanine nucleotide exchange factor (Vav) and Ras-related C3 botulinum toxin substrate (Rac) (figure 2).[75] PKCδ propagates signalling to the nucleus by activating the canonical nuclear factor of kappa light chain enhancer of activated B cells (NF-κB) pathway.[75] PKCδ is particularly important in B cell proliferation, apoptosis and tolerance.[75]

Class IA phosphatidyl-inositol-3-kinase (PI3K) isoforms are crucial signalling molecules downstream of various B cell and T cell surface receptors (figure 2).[76 77] Consequently, PI3K is involved in many aspects of B cell and T cell homoeostasis.[76 77] The PI3K pathway activates a multitude of effector molecules and is interwoven with the PLC-PKC pathway, forming a complex signalling network (figure 2).[76 77]

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The transcription factor IKAROS is a pleiotropic regulator of haematopoiesis.[78] Besides key roles in T cells and non-lymphoid lineages, IKAROS is a critical regulator of B cell lymphopoiesis and function.[78] IKAROS is triggered by (pre)antigen receptor signalling though the precise signalling pathways remain unclear (figure 2).[78]

Interferon regulatory factor 2 binding protein 2 (IRF2BP2) is thought to act as a negative regulator of the nuclear factor of activated T cells (NFAT) transcription factor (figure 2).[79] In B cell biology, IRF2BP2 might play a role in the differentiation and/or survival of memory B cells and plasmablasts.[79] However, its function and interactome remains obscure.[79]

Defects in the genes encoding PKCδ, PLCγ2, NF-κB2, NF-κB1, PI3K catalytic subunit p110δ, PI3K regulatory subunit p85α, Vav1, Rac2, BLK, IKAROS and IRFBP2 have been described in patients with CVID(-like) disease.

PKCδ deficiency

Biallelic *PRKCD* (encoding PKCδ) mutations abrogating protein expression have been described in six patients from four unrelated families.[75 80–82] *PRKCD* was detected using WES combined with homozygosity mapping or linkage analysis in consanguineous families.[75 80]

PKCδ deficiency causes a variable phenotype (table 1).[75 80–82] A CVID-like phenotype was only observed in the first-reported patient.[75] The other five patients were initially diagnosed with systemic lupus erythematosus (SLE) or ALPS-like disease.[80–82] Altogether, PKCδ deficiency represents a syndrome of immune dysregulation with prominent lymphoproliferation and systemic autoimmunity reminiscent of SLE.[75 80–82] All patients displayed an aberrant B cell phenotype with decreased switched memory B cells and increased CD21^{low} B cells.[75 80–82] However, only the first-reported patient developed hypogammaglobulinaemia and, accordingly, prominent infections.[75]

Of interest, the first-reported PKCδ-deficient patient carried an additional heterozygous *CTLA4* variant (Thr17Ala, allele frequency 0.4112), previously associated with autoimmune thyroiditis.[75] This variant was also present in the father who had Behçet's disease and autoimmune thyroiditis.[75] It cannot be excluded that this *CTLA4* variant exerts a disease-modifying effect on these individuals' phenotype.[75]

PLCγ2-associated antibody deficiency and immune dysregulation

PLCγ2-associated antibody deficiency and immune dysregulation (PLAID) is a newly defined immunodeficiency syndrome caused by heterozygous gain-of-function mutations in *PLCG2*.[83 84] *PLCG2* was identified by two independent groups, one using linkage analysis in three families combined with whole-genome sequencing (WGS) in one of those families,[83] and another using WES in a multiplex family with an autosomal dominant inheritance pattern.[84]

PLAID is mainly characterised by cold urticaria from infancy, which is not typically seen in CVID.[83] However, PLAID shares many hallmark clinical and immunological features with CVID (table 1).[83 84] Indeed, some of the initially published patients with PLAID fulfilled the diagnostic criteria of CVID.[83] This phenotypical overlap might be explained by aberrant PLCγ2 signalling downstream of the BCR and Fcγ receptors on B cells (figure 2).[83]

NF-κB2 and NF-κB1 deficiencies

The NF-κB family of transcription factors regulates a diversity of biological processes.[85 86] The (non-canonical) NF-κB2 pathway is activated by a limited set of receptors, including ICOS, TACI, BAFF-R and BCMA (figure 2).[85 86] In contrast, the (canonical) NF-κB1 pathway is targeted by a vast number of receptors, including BCR/co-receptor complex, TCR and TLRs (figure 2).[85 86] NF-κB signalling plays key roles in B cell maturation, survival, differentiation, class switching and tolerance to self-antigens.[85 86]

NF-κB2 deficiency

First described were heterozygous *NFKB2* mutations detected by WES in a multiplex CVID pedigree with an autosomal dominant inheritance.[85] In patients with mutant NF-κB2 (also known as NFKB p52/p100 subunit), the inactive precursor protein p100 fails to be phosphorylated and can therefore not be processed into its active form p52 resulting in NF-κB2 haploinsufficiency (figure 2).[85 87–91] Some *NFKB2* mutations also appear to disrupt the canonical NF-κB1 pathway through a dominant-negative effect of the unprocessed p100 protein.[87–91]

All NF-κB2-deficient patients presented with a CVID(-like) phenotype in early childhood and suffered from recurrent respiratory tract infections.[85 87–91] About half of patients developed pituitary hormone deficiencies, which is an unusual feature in CVID.[85 87–91] Two of them had pituitary hypoplasia on brain MRI scan.[87] In addition, several patients developed autoimmune manifestations involving skin, hair and/or nails. Autoimmune cytopenia, usually the predominant autoimmune manifestation in CVID, was not documented except for one child with an episode of autoimmune thrombocytopenia.[85 87–91] Furthermore, NF-κB2-deficient patients demonstrated (pan)hypogammaglobulinaemia, abnormal B cell immunophenotyping and varying degrees of T cell and NK cell abnormalities (table 1).[85 87–91]

NF-κB1 deficiency

Recently, heterozygous *NFKB1* mutations were reported in three CVID-affected families.[86] Mutant NF-κB1 protein (also called NFKB p50 subunit) was unstable and rapidly degraded resulting in NF-κB1 haploinsufficiency (figure 2).[86] *NFKB1* was identified by means of WES combined with linkage analysis in a large family with autosomal dominant inheritance.[86] In contrast to *NFKB2*, *NFKB1* mutations were also identified in relatives with milder forms of antibody deficiency (eg, sIgAD, IgG subclass deficiency) and even in some clinically healthy relatives. This could be due to incomplete penetrance, the presence of modifier genes and/or environmental factors.[86]

NF-κB1-deficient patients displayed a variable phenotype, different from that of NF-κB2-deficient patients, with variable age of onset and severity (table 1).[86] The main clinical features seen in NF-κB1-deficient patients are recurrent infections, benign lymphoproliferative disease, lymphoma, and autoimmunity including autoimmune cytopenia and enteropathy.[86] None had pituitary hormone deficiencies.[86] Furthermore, NF-κB1-deficient patients had varying degrees of hypogammaglobulinaemia, normal lymphocyte counts, and no obvious defects in innate immunity (table 1).[86]

PI3K overactivity and deficiency

PI3K p110δ overactivity

A heterozygous mutation in the gene encoding the PI3K catalytic subunit p110δ (*PIK3CD*) was initially identified in a patient with CVID in 2006 based on a mouse knockout model.[92] Since 2013, heterozygous *PIK3CD* mutations have been described in more than 50 patients using WES.[76 77 93–97] These mutations result in overactivity of the PI3K signalling pathway evidenced by enhanced p110δ membrane association and kinase

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activity.[76 77] More than half of reported cases were heterozygous for the missense mutation E1021K.[76 77 92–97] Haplotype analysis was suggestive for a recurrent rather than for a founder mutation.[76]

PI3K p110δ mutant patients showed phenotypical overlap with many other PID syndromes; the majority was diagnosed with CVID, CID or hyper-IgM syndrome.[76 77 92–97] Therefore, the phenotype associated with dominant *PIK3CD* gain-of-function mutations was regarded as a novel disease named activated PI3Kδ syndrome (APDS).[76]

The clinical spectrum of APDS varies greatly (table 1). Important is the increased risk of malignancy (eg, B cell lymphoma) even in patients with a seemingly milder phenotype.[76 77 92–97] Constitutively activated PI3K pathway causes numerous defects in B cell and T cell differentiation and function (table 1). A recurrent feature is a normal or often increased serum IgM level.[76 77 92–97]

PI3K p85α deficiency

Some patients with an APDS-like phenotype were found to have heterozygous loss-of-function mutations in *PIK3R1*, encoding the PI3K regulatory subunit p85α, by means of WES.[98–101] Up to now, all were splice site mutations resulting in loss of an exon in the domain that inhibits p110δ catalytic activity.[98–101] Loss of p85α-mediated inhibition of p110δ causes hyperactivity of the PI3K signalling pathway (figure 2) explaining the APDS-like phenotype (table 1).[98–101] Many of these cases were previously diagnosed with CVID.[98–101]

Of note, a homozygous *PIK3R1* mutation causing complete loss of p85α expression had been previously reported in a single patient born from consanguineous parents.[102] In contrast to the above-described heterozygous splice site mutations, complete loss of p85α resulted in a significant reduction of PI3K signalling causing agammaglobulinaemia and absence of B cells.[102]

Vav1, Rac2 and BLK deficiencies

A heterozygous *Vav1 guanine nucleotide exchange factor* (*VAV1*) mutation resulting in decreased protein expression was described in one patient diagnosed with CVID.[103] Since this patient showed considerable T cell dysfunction (table 1), Vav1 deficiency more likely causes CID rather than CVID.[103]

A homozygous *Ras-related C3 botulinum toxin substrate 2* (*RAC2*) mutation abolishing protein expression was identified in two siblings born from consanguineous parents.[104] Both siblings presented with IgA deficiency that gradually evolved into CVID (table 1).[104] Interestingly, heterozygous dominant-negative *RAC2* mutations cause a complex neutrophil dysfunction.[104] The Rac2-deficient patients with CVID showed less severe defects in neutrophil function.[104]

A heterozygous loss-of-function mutation in *BLK* was detected in two related patients with CVID.[105] BLK plays a role in BCR signalling and recruitment of T cell help (figure 2).[105] This may explain the disturbed terminal B cell differentiation seen in these patients (table 1).[105]

More patients will need to be identified to determine if Vav1, RAC2 and BLK deficiencies should be considered as CVID or as separate disease entities.

IKAROS deficiency

Heterozygous mutations in *IKZF1*, encoding the transcription factor IKAROS, have been very recently identified in six CVID-affected families.[78] All mutations involved the DNA-binding domain of IKAROS, resulting in failure to bind target genes and haploinsufficiency (figure 2).[78] All patients with IKAROS deficiency had been diagnosed with CVID. Although there was variation in the clinical and laboratory phenotype (table 1), the majority of IKAROS-deficient patients with CVID had panhypogammaglobulinaemia and low B cell numbers with a progressive loss of serum immunoglobulins and B cells over time.[78] In three out of six families the same genetic defect (ie, one missense variant and two large deletions) in *IKZF1* was also found in asymptomatic relatives, which suggests incomplete penetrance and could be explained by modifying genetic and/or environmental factors.[78] Note that most of the asymptomatic individuals were children, who might still develop a clinical phenotype at an older age.[78] In our CVID cohort, we identified a sibling pair with a novel heterozygous frameshift variant in *IKZF1*, also located in the DNA-binding domain. The cellular phenotype of our patients is similar to that of the published cases.[78] Further analysis is currently ongoing.

IRF2BP2 overactivity

Very recently, one family with an autosomal dominant pattern of CVID was identified with a heterozygous *IRF2BP2* mutation cosegregating with disease.[79] In vitro analyses demonstrated that the *IRF2BP2* mutation impaired plasmablast differentiation of B cells.[79] Furthermore, subjects with the heterozygous *IRF2BP2* mutation had increased levels of the corresponding transcripts and protein.[79] The findings are suggestive for a gain-of-function mutation and for an augmented repression of NFAT transcriptional activity by IRF2BP2 (figure 2).[79] However, additional studies are needed to uncover the mechanism by which the *IRF2BP2* mutation disturbs B cell biology and causes a CVID phenotype.[79]

All patients with the heterozygous *IRF2BP2* mutation were diagnosed with CVID in childhood. The main phenotypical features were recurrent sinopulmonary infections, decreased IgG (mainly IgG2), low to undetectable IgA and IgM levels, and very low memory B cells (table 1).[79] They did not display evidence of T cell dysfunction.[79]

Genes associated with other PID disorders

The first disease stages of other PID syndromes may sometimes resemble CVID. In fact, a large number of well defined PID disorders can be accompanied by antibody deficiency sometimes mimicking CVID.[106] Mutations in *GATA2*, *RAG1*, *JAK3* and *DCLRE1C* (encoding ARTEMIS), genes associated with other well defined PID disorders, were recently described in patients with a prior diagnosis of CVID.[107–111]

Autosomal dominant loss-of-function mutations in *GATA2* cause a PID syndrome typically characterised by decreased monocytes, B cells, NK cells and dendritic cells, myelodysplasia, opportunistic infections and lymphoedema.[107] In a recent report, a boy with a heterozygous *GATA2* mutation presented with hypogammaglobulinaemia and defective antibody responses in early childhood diagnosed as CVID.[107] However, during adolescence his monocyte and lymphocyte counts rapidly dropped resulting in a full-blown GATA2 deficiency syndrome.[107]

Autosomal recessive loss-of-function mutations in *RAG1*/*RAG2*, *JAK3* and *DCLRE1C* are historically associated with severe combined immune deficiency, but hypomorphic mutations are known to cause a more insidious clinical picture.[108–111] Occasionally, patients can present with early onset antibody deficiency, impaired vaccine responses and (sub)normal lymphocyte counts eliciting a diagnosis of CVID as demonstrated in recent publications.[108–111] These patients gradually developed a more severe phenotype leading to reconsideration of the prior

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CVID diagnosis and identification of biallelic mutations in *RAG1*, *JAK3* or *DCLRE1C*.[108–111]

Genetic workup in monogenic CVID

To date, there are no clinical guidelines regarding the genetic workup of patients presenting with CVID. Genetic assessment should at least be considered in patients with severe complications since this may be important to guide treatment and follow-up (eg, LRBA/CTLA-4 deficiency, APDS).[62 77 94 98] Patients with monogenic CVID would also benefit from genetic testing to support genetic counselling and reproductive options.

A monogenic cause of CVID is more likely in case of early disease onset (eg, presenting in infancy or early childhood), a positive family history or consanguinity. Most of the known monogenic forms result in decreased or absent expression of a specific protein which might direct genetic testing. Still, normal protein expression does not exclude a functional defect. If only one or a limited number of CVID genes are suspected based on the patient's phenotype (table 1), we recommend protein expression analysis (if applicable) in combination with targeted testing of a single CVID gene or of a gene panel[112] (in case of more than one possible gene). However, taking into account the large genetic heterogeneity of monogenic CVID as well as the large phenotypical overlap with other PID syndromes, clinical WES[113] will be likely recommended in the majority of suspected monogenic CVID cases. WGS is currently not employed for routine clinical purposes, but shows great potential as a clinical NGS tool.[114]

COMPLEX FORMS OF CVID

CVID, a complex disorder?

It is increasingly believed that besides rare monogenic forms, CVID is a polygenic or multifactorial disorder. This is based on the following: (1) identification of pathogenic mutations in only 2–10% of patients with CVID despite tremendous efforts, (2) large phenotypical variability between patients with the same primary genotype, (3) presence of variants in asymptomatic relatives and/or in the general population above a certain threshold frequency, (4) sporadic occurrence in about 90% of cases and (5) delayed disease onset in many patients.[4 9 19 31 60 61 86 115 116]

Widespread use of NGS technologies has fuelled the idea of a possible polygenic nature of CVID.[4 9 115 116] Van Schouwenburg *et al*[4] performed WGS in 32 sporadic patients with CVID and one grandmother-grandson pair combined with RNA sequencing of B cells in 3 sporadic patients. They observed that all patients had variants in multiple genes associated with CVID or other PID syndromes as well as an enrichment of variants in pathways important in B cell function.[4] An average of 9.4 (range 5–15) variants possibly associated with CVID were found in each patient.[4] Interestingly, predicted deleterious variants were identified in numerous genes not previously associated with CVID such as *PRRC2A*, *LILRB5*, *PSMB9*, *TNIP1*, *ARID3A*, *INPP5D*, *SH3BP2*, *BANK1*, *GAB2*, *CAMLG*, *BCL2L11* and *EBF1*.[4] Note that functional validation studies are still necessary to determine the contribution of these variants to CVID development.

In a study on a monozygotic twin pair discordant for CVID, the CVID-twin demonstrated impaired DNA demethylation in key B cell genes such as *PIK3CD*, *RPS6KB2*, *BCL2L1*, *TCF3*, *CORO1B/PTPRCAP*, *KCNN4* and *KCNC4*.[117] The B cell genes that were hypermethylated in the CVID-twin covered diverse functions of B cell biology.[117] Subsequent analysis of a larger CVID and healthy control cohort confirmed that CVID B cells had a reduced ability to demethylate these key genes during differentiation from naive to memory B cells.[117] DNA methylation is an epigenetic mechanism to control gene expression and can be influenced by environmental factors like smoking and infections.[117] The altered DNA methylation patterns in CVID B cells implicate a role for epigenetic and/or environmental factors in CVID pathogenesis.[117]

Variants associated with CVID

Certain variants seem to occur more frequently in patients with CVID and may thus be a risk factor to disease development, although they do not suffice to establish a complete phenotype. Such variants have been reported in DNA repair genes (eg, *MSH5*),[118] and in *FCGR2A*.[119] Furthermore, in individual patients with CVID, certain variants may influence the development of specific disease features like enteropathy or autoimmunity.[120–122]

Genome-wide association studies

Genome-wide association studies (GWAS) from 2011 (363 patients with CVID, 3031 controls) found an association with the human leukocyte antigen (HLA) region, consistent with findings from prior linkage studies.[116 123] These researchers also identified a suggestive but non-significant association with a chromosome 8p locus containing *ADAM28*, *ADAM7*, *ADAMDEC1* and *STC1*.[116] In addition, patients with CVID demonstrated an increased total copy number variation burden, suggesting a role for genomic instability in CVID pathogenesis.[116] Intraexonic duplications in *ORC4L* were found to be most highly associated with CVID.[116] GWAS in healthy Chinese men (n=3495) showed an association between serum IgG and the locus containing *TNFRSF13B* (encoding TACI).[124] However, the 2011 GWAS did not detect associations with the *TNFRSF13B* locus.[116]

A GWAS from 2015 (778 patients with CVID, 10 999 controls) confirmed association with the HLA locus and also found associations with loci containing *CD21*, *ICOS*, *MSH5*, *TNFRSF13B* and *CLEC16A*.[9] The *CLEC16A* locus had previously been associated with autoimmune disorders.[9] CLEC16A might provide a link between autoimmunity and B cell deficiency in CVID.[9]

GENERAL CONCLUSION

The genetic basis of CVID is gradually being unravelled mainly by the identification of disease genes for monogenic forms. However, these only explain 2–10% of patients with CVID. The role of modifier genes and environmental factors in complex forms of CVID will need to be further explored.

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