Published in final edited form as:

Ann N Y Acad Sci. 2011 December ; 1246: 41–49. doi:10.1111/j.1749-6632.2011.06338.x.

Perspectives on common variable immune deficiency

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Abstract

Common variable immunodeficiency (CVID) is considered to be a collection of genetic immune defects with complex inheritance patterns. While the main phenotype is loss of B cell function, the majority of the genetic mechanisms leading to CVID remain elusive. In the past two decades there have been increasing efforts to unravel the genetic defects in CVID. Here, we provide an overview of our current understanding of the genetic basis of these defects, as revealed over time by earlier linkage studies in large cohorts, analysis of families with recessive inheritance, targeted gene approaches, and genome-wide association studies using single nucleotide polymorphism arrays and copy number variation, and whole genome studies.

Keywords

common variable immunodeficiency; hypogammaglobulinemia; IgA deficiency; genome-wide association studies; single nucleotide polymorphism; copy number variations; recessive genes

Introduction

The programmed development and maintenance of B cells capable of producing, in great abundance for an indefinite period of time, virtually unlimited numbers of antibody specificities is one of the most enigmatic features of biology. Each step in this complex process requires a sequence of transcription factors, cell surface interactions, migratory stimuli, cytokines, and the appropriate niche locations to sponsor these events. Even when formed and functional, new B cells are subjected to continual counterselection to exclude self-reactivity and, finally, to equip emerging clones with a high degree of specificity for previously selected antigens. B cells have several fates, a prominent one being the maturation into long-lived plasma cells that are generated first in lymphoid organs and ultimately in the bone marrow, where they can survive for many years. Another fate of the appropriately activated B cell is differentiation into memory B cells, a CD40L-dependent fate that ensures continued capability to produce antibodies, even after the passage of long periods of time. The final products of selected B cells—serum immune globulins—represent about 20% of serum protein, but this does not include the extensive production of IgA, the most abundantly produced Ig, as at least 80% of IgA-secreting B cells reside in the gastrointestinal mucosa.

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Conflicts of interest The authors declare no conflicts of interest.

Considering the extensive biological effort manifest in B cell biology, it may be surprising to consider that an equally extensive network of genetic influences—some working singly, others as collective influences—must support the many stages of B cell biology. The study of B cells with single gene defects has elucidated some of the most essential components of B cell biology, especially for the early events of B cell survival and activation. However, the most common of these events—common variable immunodeficiency (CVID)—is for the most part not yet well understood, thus providing a still open field for exploration.

Patients with CVID have a marked reduction in serum levels of IgG (usually < 3 g/L) and usually IgA (< 0.05 g/L), with reductions in serum IgM in about half of all cases.^{1–6} With the loss of antibody, patients have a high incidence of infectious disease, but also paradoxically these same patients are also prone to both inflammatory and autoimmune disorders. CVID affects approximately 1/25,000 Caucasians, but the frequency among Americans of African descent is estimated to be 20-fold lower.⁷ CVID has been recognized for more than six decades,⁸ and while it is considered to be a genetic immune disease, family members of CVID patients are usually normal, suggesting more complex inheritance for most subjects. As the hallmark of CVID is loss of humoral immunity, the World Health Organization classifies this immune defect among the B cell defects; however, variably impaired T cell, monocyte, and dendritic cell functions have been long described, suggesting that this syndrome bears some resemblance to combined immune defects.

In the past two decades, there have been a number of attempts to unravel the genetic defects in CVID. These have included earlier and more modern genome-wide studies, index families with multiply affected members, families with inheritance of recessive genes important in B cell development, and targeted gene approaches. Here, we review these and describe some of the newly emerging themes in this field (see Fig. 1).

Earlier genome-wide linkage and family studies

While CVID is not commonly found in more than one member of a family, for about 10% of subjects other first-degree relatives may be either hypogammaglobulinemic or may have selective IgA deficiency (IgAD).^{9,10} A number of earlier studies concentrated on these families, which revealed several putative susceptibility loci. Concentrating first on families with selective IgA deficiency, Vo echovský *et al.* examined 101 multiple-case families, containing a total of 554 informative family members, with IgA deficiency and CVID and identified susceptibility loci within the HLA region on chromosome 6p.¹¹ Linkage analysis of this cohort indicated a putative susceptibility locus termed *IGADI*. Of the 110 haplotypes shared by 258 affected family members, a single haplotype accounted for the majority of *IGADI* contributions to the development of IgAD/CVID in this cohort. For unclear reasons, in this data set affected mothers transmitting the phenotype to their offspring were overrepresented compared to affected males, although this was not apparent in multiple-case families with a predominance of affected mothers (however, it should be noted that previous work suggested that the offspring of IgA-deficient mothers may not develop IgA due to transplacental transmission of anti-IgA antibodies).¹² Subsequent work also suggested that selected *HLA-DQ/DR* haplotypes conferred either protection or susceptibility to IgAD and CVID.¹³ The strong influence of the MHC region was more recently noted in several other cohorts; in one, the majority of patients inherited HLA *DQ2, *DR7, *DR3 (17), *B8, and/or *B44. B44 was present in almost half, and was the most common susceptibility allele.¹⁴ A strong influence of the MHC region was again recently noted in whole-genome studies, described in detail below.¹⁵

Reinvestigating the same cohort as Vo echovský *et al.* but restricting the focus to families in which at least one case of CVID was known, another study suggested linkage of autosomal

dominant CVID to chromosome 16q.¹⁶ A candidate gene considered here was *WWOX* (WW-domain containing oxidoreductase), but no mutations were found. As described below, a large heterozygous deletion in this same region was later noted for one subject in wholegenome studies, suggesting the need for additional studies of this region.¹⁵

Further studies examined another extended family with autosomal inheritance pattern of immune deficiency. In this family, six cases of CVID—five of IgAD and three of dysgammaglobulinemia—over five generations were found.¹⁷ Linkage analysis performed on this family identified an area of interest on chromosome 4. Further genotype analysis of nine markers on chromosome 4q was used to find similar markers in 32 additional families, suggesting the existence of a disease-causing gene for autosomal-dominant CVID/IgAD in this region. The authors suggested several candidate genes, including *DAPPI*, a B cell signaling molecule, mutation of which leads to IgG3 deficiency in mice, and *BANK1*, which plays a role in B cell response to antigens,¹⁸ but these have also not been validated.

Recessive genes important for B cell development

Some of the most incisive advances in CVID have more recently emerged from studies of families with a consanguineous background, demonstrating that mutations in single genes important in B cell biology can lead to the CVID phenotype.

Inducible costimulator

The inducible costimulator (ICOS) is a cell surface receptor structurally and functionally closely related to CD28¹⁹ and expressed on activated T cells. Functionally, ICOS is important for the production of IL-10, a cytokine implicated in the generation of B cell memory and plasma cells.^{20–23} Grimbacher *et al.* described a homozygous deletion of ICOS gene (*ICOS*) inherited as an autosomal recessive trait in four CVID related patients.²⁴ As interaction of ICOS with its unique ligand ICOS-L plays an important role in T cell help for late B cell differentiation, class-switching, memory B cell generation, and the numbers of memory and switched memory B cells were substantially reduced in the patients with *ICOS* deletion, as were serum immunoglobulin concentrations. Thus, ICOS deficiency resulted in defective T cell help for late B cell differentiation, suggesting an explanation for the clinical phenotype of CVID in these subjects. Extending this work, Salzer *et al.* identified other individuals in the same kindred, all of whom carried the identical large genomic deletion of *ICOS*.²⁵ Later, Takahashi *et al.* reported an in-depth analysis of T cell function in two siblings with ICOS deficiency.²⁶ While the brother displayed mild skin infections and impaired immunoglobulin class switching, the sister exhibited more severe manifestations, including immunodeficiency, inflammatory bowel disease, interstitial pneumonitis, rheumatoid arthritis, and psoriasis. Their work demonstrated an extensive T cell dysfunction, decreased memory T cell compartment, and an imbalance between effector and regulatory cells that may underlie immunodeficiency and/or autoimmunity observed in the sister. While mutations of the ICOS-L gene (*ICOSLG*) could theoretically lead to a similar CVID phenotype, subjects bearing such a mutation have not been identified.

CD19 deficiency

Four surface proteins (CD19, CD21, CD81, and CD225) on the surface of mature B cells form a complex that signals in conjunction with the B cell antigen receptor, thereby decreasing the threshold for activation by antigen.²⁷ Of these, CD19 appears early and remains on B cells during differentiation until maturation into plasma cells. In 2006, van Zelm *et al.* reported four patients from two unrelated families who had hypogammaglobulinemia and mutation of the *CD19* gene.²⁸ One patient, from Turkey, had an insertional mutation in both alleles of *CD19* leading to a frame shift, while three other

patients, adult hypogammaglobulinemic siblings from Colombia, were homozygous for deletion resulting in a premature stop codon in the intracellular domain. In these patients, CD27⁺ memory B cells were decreased, and the response of the patients' B cells to *in vitro* stimulation through the B cell receptor was impaired, as was antibody response to rabies vaccination. The patients were on immunoglobulin replacement, but antibody deficiency was documented *de novo*. Another case of CD19 deficiency was described a year later in a Japanese patient with CVID.²⁹ This patient, who had a very similar clinical phenotype as other patients with CD19 deficiency, had a compound heterozygous mutation in *CD19*, both of which were novel mutations. More recently in 2011, two additional patients with CD19 deficiency from two different families were reported.³⁰ One of these patients was a girl of Moroccan descent born to consanguineous parents who demonstrated selective IgG1 deficiency, conserved antibody response against protein antigens on vaccination, and, interestingly, glomerulonephritis consistent with a diagnosis of IgA nephropathy.

CD81 deficiency

As CD81 forms a part of CD19 complex, it may not be surprising that mutations of CD81 could mimic the defects of *CD19*. This was demonstrated by van Zelm *et al.*, who reported the first case in a six-year-old girl born to consanguineous parents.³¹ Similar to the CD19-deficient patients reported earlier, she had hypogammaglobulinemia, decreased memory B cell numbers, impaired specific antibody responses, and an absence of CD19-expressing B cells. The sequence analysis demonstrated normal *CD19* alleles but a homozygous splice site *CD81* mutation resulting in a complete lack of CD19 protein expression. The requirement of intact *CD81* for *CD19* expression and function was also validated in CD81-knockout mice, which demonstrated that *CD19* expression is reduced on mature B cells and antibody production in response to T cell-dependent antigens is impaired.^{32–34}

CD20 deficiency

CD20, one of the first B cell-specific differentiation antigens identified,³⁵ belongs to the membrane-spanning 4-domains (MS4A) family of molecules³⁶ and is expressed on pre-B and mature B cells but is lost upon differentiation into plasma cells.³⁷ While CD20 is likely involved in the regulation of B cell activation and proliferation,^{38,39} its precise role in B cell physiology has remained elusive. In 2010, Kuijpers *et al.* reported a young Turkish patient, born to a consanguineous marriage, with CD20 deficiency due to a homozygous mutation in a splice junction of the CD20 gene (*MS4A1*) resulting in nonfunctional mRNA species.⁴⁰ The clinical features of this patient overlapped with CVID, namely, persistent hypogammaglobulinemia, recurrent bronchopneumonia, reduction in memory B cells, and markedly reduced ability to respond to pneumococcal polysaccharides. Additional cases of mutations in the CD20 gene remain to be found.

BAFF-R deficiency

B cell activating factor receptor (BAFF-R), a member of the TNF receptor superfamily, is encoded by three exons of the *TNFRSF13C* gene located on chromosome 22q13.^{41,42} BAFF, also called BLyS, is a ligand of BAFF-R, and studies have demonstrated the importance of BAFF/BAFF-R interaction in B cell survival. Mice deficient in either BAFF or BAFF-R are characterized by a block of B cell development at the transitional stage.^{43–48} Initial attempts to identify potential mutations in *BAFF-R* led to sequencing of the *BAFF-R* gene in patients with CVID who had very low B cell numbers. These demonstrated three novel variants present at the heterozygous state leading to amino acid substitutions.⁴⁹ These variants, however, were found to be polymorphic variants as they had no effect on the expression of the *BAFF-R* gene both at the mRNA and protein level. A few years later, Warnatz *et al.* identified two adult siblings (but one with CVID), born to a consanguineous marriage, carrying a homozygous deletion in the *BAFF-R* gene, resulting in undetectable

BAFF-R expression.⁵⁰ One sibling had low serum immunoglobulins (IgG and IgM, but normal IgA) and poor antibody responses to protein vaccines and pneumococcal polysaccharides. The other, who was clinically well, had only a slightly reduced serum IgG and IgM, but preserved antibody production to tetanus, showing some discordance. The authors concluded that deletion of the *BAFF-R* gene causes a characteristic immunological phenotype, but it does not necessarily lead to a clinically manifest immunodeficiency state.

Transmembrane activator and calcium-modulating cyclophilin ligand interactor mutations

Transmembrane activator and calcium-modulating cyclophilin ligand interactor (TACI) is expressed on mature B cells and binds its ligands BAFF and APRIL (a proliferation-inducing ligand). The activation of TACI leads to T cell-dependent and T cell-independent responses and isotype switch.^{51–53} TACI is encoded by *TNFRSF13B*, and knockout mice (*TNFRSF13B*^{-/-}) develop a lymphoproliferative disorder, autoimmunity, and splenomegaly, suggesting, in addition to its role in B cell activation, an inhibitory role of TACI in signaling.^{54–56} Using a candidate gene approach, Salzer *et al.* reported the mutations in *TNFRSF13B* encoding TACI in 13 individuals with CVID.⁵⁷ They demonstrated homozygosity for several coding variants (C104R, A181E, and S144X); in addition, heterozygous coding variants (C104R, A181E, S194X, and R202H) were identified. At the same time, Castigli *et al.* noted similar findings, and demonstrated dominant inheritance in other cohorts.⁵⁸ In general, mutations in *TNFRSF13B* are found in about 8% of CVID patients.^{59,60} The extracellular mutation, C104R, and a transmembrane, A181E, constitute a majority of mutations identified, with heterozygosity occurring far more common than homozygosity. C104R leads to a disruption of a region important for binding the ligands, BAFF, and APRIL; the transmembrane mutations are presumed to lead to impaired BAFF and APRIL signaling. While TACI mutations are significantly associated with the CVID phenotype,⁶⁰ and in these subjects with both autoimmunity and lymphoid hyperplasia, some of the same mutations can be found in clinically healthy relatives, suggesting the role of other factors.⁵⁹ Even homozygous mutations in C104R did not lead to hypogammaglobulinemia in one of the three siblings of a family in which both parents bore one heterozygous mutation.⁶¹ Thus mutations in *TNFRSF13B*, while biologically of great interest, are not diagnostic for CVID or predictive of the development of this immune defect, suggesting that routine testing for *TNFRSF13B* mutations is not recommended for these purposes.

Other targeted gene approaches

Along with family studies, there have been a number of attempts to extend an understanding of CVID by investigating if mutations in selected genes important in B cell development could be identified. Seeking mutations or polymorphisms in IL-10,^{62,63} IL-10 receptor, IL-21, and IL-21 receptor,⁶⁴ all cytokines important for B cell maturation, has not proven fruitful thus far. The chemokine receptor gene *CXCR4*, mutated in WHIM (warts, hypogammaglobulinemia, infections, myelokathexis) syndrome, has also been investigated as alternative phenotypes, not including warts, that could lead to forms of CVID, but was not found mutated in one large group of subjects (Cunningham-Rundles, unpublished data).

Single nucleotide polymorphisms and copy number studies

Extensive genome-wide association studies (GWAS) using single nucleotide polymorphism (SNP) arrays have recently enabled high-throughput genotyping of genomic DNA and investigation of copy number variations (CNVs). A 2010 GWAS study of IgAD patients from Sweden and Iceland identified associations with variants in *IFIH1* and *CLEC16A*, both known to be associated with autoimmune disease, as well as associations with class II alleles in the HLA region.⁶⁵ The first GWAS SNP and CNV study on CVID patients collected from

four medical centers investigated 610,000 SNPs of 363 CVID subjects compared to 3,031 controls.¹⁵ Again, a strong association with the MHC region was revealed, and associations with the disintegrin and metalloproteinases 28 (*ADAM28*), *ADAM7*, *ADAMDEC1*, and stanniocalcin-1 (*STC1*) were suggested. Recent studies have noted that CVID is characterized by fairly stereotypic phenotypic patterns associated with selected inflammatory/autoimmune medical complications.^{1,2,6,66–69} Thus, the CVID subjects were classified by these phenotypes, including cancers, lymphoma, lymphadenopathy, nodular regenerative hyperplasia of the liver, lymphoid interstitial pneumonitis (LIP), bronchiectasis, biopsy-proved granuloma, gastrointestinal enteropathy, malabsorption, splenectomy, cytopenias, organ-specific autoimmunity, low IgM (<50 mg/dL), low IgA (<10 mg/dL), low B cell number (CD19⁺ cells <1%), and young age at symptom onset (<10 years).¹⁵ SNP analysis revealed genes associated with particular phenotypes, including mitogen-activated protein kinase kinase kinase 7-interacting protein 3 (*MAP3K7IP3*), significantly associated with low IgA. Genes significantly associated with lymphoma included *PFTK1*, *HAVCR1*, and *KIAA0834*. The gene *CACNA1C* (calcium channel, voltage-dependent, L-type, alpha 1C subunit) was found associated with gastrointestinal enteropathy.¹⁵

In addition to SNP investigation, CNV analyses uncovered several novel genes that were significantly associated with CVID. Of these, 84 CNV deletions and 98 duplications were identified in one or more patients, but were not found in any of the 2,766 control subjects. Some of these also overlapped with the GWAS part of the study. Five deletions and 11 duplications were found to be recurrent in the patient group and were significantly increased in CVID cases compared with controls; 15 regions were unique to CVID cases. Specifically, a significant number of subjects had duplications in *ORC4L*, which is essential for initiation of DNA replication in immune cells and has previously been associated with B cell lymphoproliferative disorders.⁷⁰ Examination of the overall CNV burden of both large (100 kb) and rare (<1%) CNVs revealed that deletions were significantly enriched in CVID cases, and all but five of the 182 CNVs, exclusive to the CVID cohort, were intraexonic.¹⁵ These findings suggest that CNVs may represent alterations in genes that could disrupt normal genetic and/or cellular function in individual subjects with CVID.

DNA gene repair in CVID

In the process of class switch recombination and somatic hypermutation, a developing B cell undergoes multiple rounds of DNA double-stranded breaks, which must be repaired or the damage will lead to apoptosis. However, B cells have evolved numerous signaling pathways that lead to repair and permit proliferation of intact B cells.^{71,72} While a number of DNA repair defects have been characterized, it is interesting that a number of them, such as defects of RAG1 or RAG2, Artemis, *Cernunnos*, ligase 4, and Nijmegen breakage syndrome, lead to a loss of B cells, and in some cases loss of T cells. Under normal circumstances, B cells undergo class switch recombination to produce a functionally diverse antibody repertoire. This process is catalyzed by activation-induced cytidine deaminase (AID) and uracil-DNA glycosylase (UNG); mutations in these account for two of the versions of the hyper-IgM syndrome.^{73–75} With inappropriate DNA repair, a predisposition to radiation damage and cancer are plausible outcomes. As CVID subjects have an increased propensity to cancer (lymphoma in particular)^{76,77} and appear to have increased cellular radio sensitivity,^{78–80} it is plausible that DNA gene repair variations could also account for some forms of CVID. In this vein, and returning to the MHC theme previously observed in CVID, Sekine *et al.* examined genetic variations in MSH5, a member of the mutS family of proteins involved in DNA mismatch repair and encoded in the MHC region. Several unique alleles of MSH5 were shown to have genetic associations with both CVID and IgAD.⁸¹ More recently, Offer *et al.* surveyed 27 candidate DNA metabolism genes and found that other markers in several mismatch repair proteins were associated with IgAD/CVID.⁸²

Resequencing was used to investigate these genes, and four rare, nonsynonymous alleles were found associated with IgAD/CVID: two in MutL homolog 1 (*MLH1*), one in *RAD50*, a protein involved in DNA double-strand break repair, and one in Nijmegen breakage syndrome 1 (*NBN*). A premature RAD50 stop codon identified in one conferred an increased sensitivity to ionizing radiation.⁸²

Conclusions

CVID is a complex, multifocal disease, the genetic origins of which are beginning to be at least partially understood. Further large cohort studies using whole-exome sequencing and other high-throughput methods, along with international studies with subjects from diverse genetic backgrounds, will be needed in the future to illuminate the many causes of this disease and possibly therapeutic targets.

Acknowledgments

This work was supported by the National Institutes of Health, AI 101093, AI-467320, AI-48693, NIAID Contract 03-22, and the David S. Gottesman Immunology Chair.

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Figure 1.

Genetics of CVID. This figure summarizes the evolution of various attempts at deciphering the genetics of CVID. The numbers on the left indicate the year of publication for each phase of the discovery.