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The Genetic Heterogeneity of Common Variable Immunodeficiency (CVID): An Update

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Abstract

B cells are generated in the bone marrow and then enter the periphery, where the maturation process takes place leading to the formation of an effective humoral immune response. Defects in this highly regulated process in the periphery have been considered to be responsible for the pathogenesis of Common Variable Immunodeficiency (CVID) for more than 6 decades. CVID is traditionally characterized by low immunoglobulin serum levels and defective antibody response in the presence of normal peripheral B cell numbers. The clinical spectrum of CVID is highly variable, including recurrent infections, autoimmune complications and increased susceptibility to cancer and lymphomas. However, only in the last decade, the genetic defects underlying this maturational B cell defect have been partially elucidated in a small percentage of affected patients. This review will focus on the current state of art regarding the known genetic alterations associated with the pathogenesis of CVID.

Keywords: Genetic heterogeneity; Immunodeficiency; Common variable immunodeficiency

Introduction

B cells are generated in the bone marrow and after sequential steps of maturation, immature B cells expressing surface IgM enter the periphery [1-4]. Antigen encounter in the periphery leads to B cell maturation giving raise to memory B cells and plasma cells [5-7]. Animal models and in vitro experimental systems have allowed for a better understanding of the mechanisms that regulate this highly specific process. These achievements have been crucial for understanding the molecular basis of different forms of humoral immuno deficiencies including Common Variable Immunodeficiency (CVID) which is the object of this review.

CVID is traditionally characterized by low immunoglobulin serum levels and defective antibody response, in the presence of normal peripheral B cell numbers. The spectrum of clinical manifestations of CVID includes recurrent infections, mainly of the respiratory and gastrointestinal tract, autoimmune phenomena ranging from autoimmune thyroiditis to Systemic lupus erythematosus (SLE), autoimmune cytopenias, splenomegaly, granulomata and increased susceptibility to cancer and lymphomas [8]. The age of onset is variable, with higher prevalence during the second and third decade of life; both sexes are involved in an equal manner. Long term follow-up of numerous cohorts of CVID patients has provided evidence for the great heterogeneity of this disorder [8], both at the clinical and immunological level, suggesting that CVID, can be considered a collection of primary immunodeficiency diseases all sharing a common immunological phenotype (i.e. low immunoglobulin serum levels, defective antibody response in the presence of normal peripheral B cell counts), which is caused by different genetic defects. This diverse genetic background offers insight regarding both the clinical heterogeneity of CVID and the immunological differences, beyond the classical immunological presentation, revealed recently through more detailed and advanced immunological evaluations.

The first case of CVID was described in 1953 by Janeway et al. [9], but it was only in 2003 that the first genetic defect associated with this disorder was identified [10]. In four CVID patients, the expression of ICOS (Inducible T-cell Co-stimulator), a T cell receptor that binds ICOS-ligand (ICOSL) expressed on B cells, was lacking due to a homozygous deletion of exon 2 and 3 from the ICOS encoding gene [10]. Lymphonode analysis from an ICOS deficient patient further underlined the importance of ICOS in the germinal center reaction and in B cell homeostasis in general [11].

In recent years, and following the candidate gene approach, three additional genes were identified to be associated with the pathogenesis of CVID in humans: TNFRSF13B, TNFRSF13C, CD 19. In 2005, two different groups identified mutations in TNFRSF13B encoding for TACI, to be associated with CVID in humans [12,13]. Salzer et al. [13] screened 162 unrelated CVID cases for mutations in TNFRSF13B and identified 5 mutations: C104R, S144X in the homozygous state and C104R, A181E, S194X and R202H in the heterozygous state. FACS analysis showed that the mutations in the homozygous state S144X and C104R resulted in lack of B-cell TACI expression and lack of binding to APRIL but not to BAFF, since the expression of the BAFF receptor (BAFF-R) was unaltered. Furthermore, APRIL and BAFF failed to induce class-switch recombination in TACI-deficient B cells. A severe decrease in IgD-negative (i.e., class-switched) memory B cell numbers wasnoted, but no distinct abnormal B-cell phenotype as observed in Tnfrsf13b -/- mice, which have an expanded population of circulating mature peripheral B cells, was observed in the mutated patients [14]. The other variants in the heterozygous state (C104R, A181E, S194X and R202H) were reported to be associated with defective antibody production. They also reported that CVID patients with TNFRSF13B mutations had a somewhat higher frequency of autoimmunity and presented the HLA-B8-DR3-DQ2 ancestral haplotype which has been found associated with selective IgA

deficiency (SIgAD). Interestingly, Castigli [12] found TNFRSF13B mutations both in patients with CVID and SIgAD supporting the hypothesis that CVID and SIgAD may share similar pathogenetic mechanisms.

The role of TNFRSF13B coding variants in CVID and SIgAD was recently re-examined. Pan-Hammarstrom et al. [15] provided supporting evidence that heterozygous C104R, A181E and in s204A sequence variants in TNFRSF13B constitute risk factors for the development of CVID rather than being causative genes. Furthermore, their data suggested that these variants had only minor roles, if any, in the development of IgAD. Castigli et al. [16] presented additional data supporting their initial conclusion that TNFRSF13B coding variants, especially C104R and A181E, are associated with CVID.

The spectrum of TNFRSF13B mutations in CVID is continuously expanding. In fact, the novel compound heterozygous mutation I87N/C104R, that leads to aberrant TACI expression and abrogates APRIL binding on EBV B cells, was recently identified in two brothers with hypogamma globulinaemia and respiratory and gastrointestinal infections [17].

Further studies were undertaken in order to better define the biological significance of TNFRSF13B variants in patients affected with CVID. Salzer et al. [18] identified that at least one TNFRSF13B variant allele was present in 50 (8.9%) out of the 564 unrelated patients with antibody deficiency. Of these 50 patients, 2 (4%) carried homozygous mutations (C104R, A181E), 7 (14%) carried compound heterozygous mutations (Y79C/I87N, c.204insA/C104R, C104R/C104Y, C104R/Y164X, C104R/c.571insG, G152E/A181E), and 41 (82%) carried heterozygous mutations in the TNFRSF13B gene (C104R, A181E, D41H, Y79C, I87N, c.121delG, c204insA, A149T, C193X, V246F). The most common alleles were C104R and A181E, found in 26 (4.6%) and 13 (2.3%) patients, respectively. Only these 2 alleles were observed in a homozygous state, each in 1 individual. Among 675 controls, 7 (1%) were heterozygous for A181E, and 6 (0.9%) were heterozygous for C104R. Statistical analysis showed that a mono- or biallelic TNFRSF13B allele conferred a relative risk of 3.6 for developing hypogamma globulinaemia. The association was particularly strong for C104R (relative risk of 4.2), but not for A181E. Patients with TNFRSF13B mutations were more likely to have manifestations of autoimmunity, usually thrombocytopenia, or lympho proliferation compared to those without mutations. In conclusion, the pathogenetic role of TNFRSF13B variants is clear when they abrogate the expression of the protein on B cells, while the role of heterozygous variants is still in debate, and are most likely considered to be associated rather than causative of CVID.

Based on the role of BAFF, APRIL and their receptors (TACI, BCMA and BAFF-R, the latter being a receptor only for BAFF) on B cells function as shown in animal models, as well as of other genes important for B cell homeostasis, our group and others investigated the following candidate genes: TNFRSF13C (encoding BAFF-R), TNFSF13B (encoding BAFF), TNFSF13 (encoding APRIL), TNFRSF17 (encoding BCMA), IL10, IL10Ra, IL10Rb, IL21, IL21R and CCL18. TNFRSF13C analysis in 48 patients [19] revealed three novel variants, all at the heterozygous state: P21R, G64V and H159Y that are considered as single nucleotide polymorphisms (SNPs). However, the P21R variant was recently found to alter the polymerization of BAFF-R on the surface of B cells, contributing therefore to the pathogenesis of CVID [20]. TNFSF13B analysis showed the presence of only one novel synonymous variant, V63V, in a single patient in the heterozygous state [21]. Two novel SNPs were identified in exon 5 and exon 8 of the IL21R gene (T46M and R275Q respectively), which segregated with the disease phenotype in one CVID family. Eleven additional SNPs in the genes encoding BCMA (S81N, T159T, T175T, K179Q), APRIL (G67R, N96S), IL10 (3'UTR rs3024496), IL10Rα (A153A, I224V), IL21 (C78C) and IL21R (5'UTRrs961914) were observed at similar frequencies as in healthy controls. In conclusion, no significant association was found between the variants described above and CVID [22].

In 2006, four patients with a clinical and immunological phenotype compatible with CVID were identified to carry homozygous mutations in CD19 [23]. One patient harboured the homozygous insertion 972 in s(a) while the other three patients harboured the homozygous deletion 1384 del(ga), all leading to premature stop codons. It is well established that CD19 functions in a complex with CD21, CD81, and CD225 to signal with the B cell receptor upon antigen recognition. Levels of CD19 were undetectable in one patient and substantially decreased in the other three. Levels of CD21 were decreased, whereas levels of CD81 and CD225 were normal, in all four patients. Numbers of CD27+ memory B cells and CD5+ B cells were decreased. Secondary follicles in lymphoid tissues were small to normal in size and had a normal cellular composition. The response of the patients' B cells to in vitro stimulation through the B-cell receptor was impaired, and in all four patients, the antibody response to rabies vaccination was poor [23]. More recently two novel CD19 gene disruptions resulting in acompound heterozygous mutation, each present in one of the patient's parents, were described in an 8-year-old Japanese boy [24]. Flow-cytometric analysis demonstrated absence of CD19 and reduced CD21 expression on CD20-positive peripheral blood B cells. Mutation analysis of CD19 revealed a mutation in the splice acceptor site of intron 5 (IVS5-1G>T) of the maternal allele, resulting in skipping of exon 6, and a truncated protein product. The paternal allele was disrupted by a gross deletion encompassing at least the ATP2A1, CD19 and NFATC2IP genes [24].

Recently, mutations in TNFRSF13C, the gene encoding for BAFF-R,were found to be associated with adult-onset CVID [25]. Two siblings with low peripheral B cell counts were identified with a homozygous 24bp in-frame deletion (del 89-96) located in exon 2 of the TNFRSF13C gene.Both siblings had lower IgG and IgM serum levels but, unlike most CVID patients, normal IgA concentrations. They also did not mount a T-independent immune response against pneumococcal cell wall polysaccharides but only one BAFF-R-deficient sibling developed recurrent infections and was put on replacement treatment with immunoglobulins.

The first patient with a defect in CD20 carrying a compound mutation of the non-canonical splice donor sequence of exon 5 of the CD20 gene was recently identified [26]. Antigen-independent B cell development occurred normally in the absence of CD20 expression; however, antibody formation, particularly after vaccination with T-independent antigens, was strongly impaired in the index patient. Consistent with this, T-independent anti-polysaccharide B cell responses are severely impaired in CD20-deficient mice [26].

As mentioned above, in several patients, mutations in CD19 have been found to cause CVID, demonstrating the critical role for the protein encoded by this gene in antibody responses. However, the lack of CD19 expression on B cells doesn't necessarily result from mutations in the CD19 gene. In fact Van Zelm et al. [27] described a patient with severe nephropathy and profound hypogamma globulinaemia with decreased memory B cell numbers, impaired specific antibody responses, and absence of CD19 expression on B

cells. The patient had normal CD19 alleles but carried a homozygous c.561+1G>A mutation in the CD81 gene resulting in a complete lack of CD81 expression on blood leukocytes. Retroviral transduction and glycosylation experiments on EBV-transformed B cells from the patient revealed that CD19 membrane expression critically depended on CD81. Similar to CD19-deficient patients, CD81-deficient patients had B cells that showed impaired activation upon stimulation via the B cell antigen receptor but no overt T cell subset or function defects.

CD21 is a receptor for C3d-opsonized immune complexes and enhances antigen-specific B-cell responses. The murine knock-out model for CD21 has been reported to show impaired humoral immune responses, suggesting that defects in CD21 may be involved in the pathogenesis of CVID. Along these lines, undetectable expression of CD21 was found in a 28-year-old man with recurrent infections, reduced class-switched memory B cells, and hypogamma globulinaemia. Expression of CD19, CD81 and CD35 (product of alternative splicing from the same genetic locus encoding for CD21) was preserved. Binding of C3d-containing immune complexes and EBV-gp350 (the ligand of CD21) to B cells was severely reduced. Sequence analysis revealed a compound heterozygous deleterious mutation in the CR2 gene (encoding CD21) (c.1225+1G>C/W766X). Functional studies with anti-immunoglobulin and C3d-containing immune complexes showed a complete loss of costimulatory activity of C3d in enhancing suboptimal B-cell receptor stimulation. Vaccination responses to protein antigens were normal, but the response to pneumococcal polysaccharide vaccination was moderately impaired [28].

Gene	Chromosome	Protein	Transmission	Onset	Prevalence in CVID
ICOS	2q33.2	ICOS	Autosomal recessive	Early and late	1%
TNFRSF13B	17p11.2	TACI	Autosomal recessive/dominant	Early and late	8-10%
CD19	16p11.2	CD19	Autosomal recessive	Early and late	1%
TNFRSF13C	22q13.2	BAFF-R	Autosomal recessive	Late	<1%
MS4A1	11q12.2	CD20	Autosomal recessive	Early	<1%
CD81	11p15.5	CD81	Autosomal recessive	Early	<1%
CR2	1q32.2	CD21	Autosomal recessive	Late	<1%
PRKCD	3p21.1	PRKCD	Autosomal recessive	Early	<1%
LRBA	4q31.3	LRBA	Autosomal recessive	Early	<1%

Table 1: Summary of the genes reported to be causative of/associated with Common Variable Immunodeficiency (CVID)

All the genetic defects so far described to be associated or causative of CVID are related to receptors expressed on the cell surface. More recently, novel genetic defects affecting cytoplasmic proteins have been reported to be causative of CVID and/or autoimmune disorders. Salzer et al. [29] reported on a single patient from consanguineous family, with progressive B cell lymphopenia, hypogamma globulinaemia and severe autoimmunity, caused by protein C kinase δ (PRKCD) deficiency [29]. The homozygous mutation identified in this index patient (c.1352+1G>A) affected a splice site leading to absent expression of the encoded protein. PRKCD deficiency due to a R614W homozygous deleterious mutation was also reported in a single patient with chronic, low-grade Epstein-Barr virus infection [30]. The patient had chronic lymphadenopathy, splenomegaly, auto-antibodies, elevated immunoglobulins and natural killer dysfunction. The G510S homozygous mutation in PRKCD was identified in three patientsaffected with systemic lupus erytematosous, with B cell defective apoptosis and hyper-proliferation [31]. On the whole these data suggest that PRKCD mutations alteringB cell homeostasis, lead to variable clinical phenotypes ranging from CVID to lympho proliferation and to autoimmune disorders variably associated with hyper gamma globulinaemia.

LRBA (lipopolysaccharide responsive beige-like anchor protein) deficiency is the most recently identified genetic defect leading to CVID and/or autoimmune disorders [32-33]. Lopez-Herrera et al. [32] identified five CVID patients harbouring homozygous mutations (I2657S, R1683X, E59X and homozygous deletion including exons 1 and 2) in the gene encoding for LRBA that resulted in the loss of protein expression. All patients had early onset hypogamma globulinaemia and severe autoimmune manifestations. Their immunological findings were characterized by disturbed B cell development, defective in vitro B cell activation, immunoglobulin secretion and proliferation, and defects in B cell autophagy. LRBA deficiency due to a homozygous deletion from exon 1 to exon 30 was recently reported in a single patient with autoimmunity but without hypogamma globulinaemia, underlying that LRBA defects may present with variable immunological phenotypes [33].

Genes involved in the DNA repair process have also been implicated in the pathogenesis of CVID. This is the case of Msh5, a gene encoded in the central MHC class III region, and of its obligate heterodimerization partner Msh4 that have a critical role in regulating meiotic homologous recombination. Sekine et al. [34] presented evidence that the human MSH5 alleles containing two non-synonymous polymorphisms (L85F/P786S), may be involved in the pathogenesis of selective IgA deficiency and common variable immune deficiency (CVID).

Conclusion

In conclusion, the scientific achievements of the last decade have shed light in the genetic mechanisms involved in the pathogenesis of CVID, have added important information on B cell biology in humans and have contributed to improve patients' clinical management. The majority of the genetic defects so far identified refer to genes encoding for molecules acting as surface receptors (mainly for B cells), as cytoplasmic proteins involved in signalling cascades, or involved in the DNA repair process.Nonetheless, the genetic defects so far identified account only for 12-15% (Table 1) of CVID cases while the majority of affected patients do not have yet a definite genetic diagnosis.

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