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

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Introduction

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.

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 autoimmunity and presented the HLA-B8-DR3-DQ2 ancestral haplotype which has been found associated with selective IgA
deficiency (SlgAD). Interestingly, Castigli [12] found TNFRSF13B mutations both in patients with CVID and SlgAD supporting the hypothesis that CVID and SlgAD may share similar pathogenetic mechanisms.

The role of TNFRSF13B coding variants in CVID and SlgAD was recently re-examined. Pan-Hammerstrom 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 globulinæmia 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, c.204insA, 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 homozygous 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 globulinæmia. 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 autoimmune, usually thrombocytopenia, or lymphoproliferation compared to those without mutations. In conclusion, the pathogenetic role of TNFRSF13B variants is clear when they abreage 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 H1159Y 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), IL10Ra (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 a compound 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 (IVSS-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 b9-96) located in exon 2 of the TNFRSF13C gene. Both siblings had low 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 globulinæmia 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 MS4A1 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).

<table>
<thead>
<tr>
<th>Gene</th>
<th>Chromosome</th>
<th>Protein</th>
<th>Transmission</th>
<th>Onset</th>
<th>Prevalence in CVID</th>
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<tr>
<td>ICOS</td>
<td>2q33.2</td>
<td>ICOS</td>
<td>Autosomal recessive</td>
<td>Early and late</td>
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<td>TNFRSF13B</td>
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<td>CD19</td>
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<tr>
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<td>BAFF-R</td>
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<tr>
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<td>&lt;1%</td>
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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 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.

References