Clinical & Experimental Immunology
The Journal of Translational Immunology
British Society for immunology

Clinical and Experimental Immunology | IMMUNODEFICIENCIES | doi:10.1111/cei.12491

Common variable immunodeficiency (CVID): new genetic insight and unanswered questions

H. D. Ochs
University of Washington and Seattle Children's Research Institute, Seattle, WA, USA
Correspondence: H. D. Ochs.
E-mail: hans.ochs@seattlechildrens.org

Common variable immunodeficiency (CVID) is a clinically and molecularly heterogeneous disorder with a varied clinical presentation [1]. The age of onset varies from early childhood to much later in life, and the disease is characterized by recurrent bacterial infections, hypogammaglobulinaemia and impaired antibody responses. In addition to recurrent infections, which can be mild or serious, CVID patients often develop inflammatory and autoimmune disorders, malignancies and systemic granuloma formation, as well as gastrointestinal (GI) problems [2]. Most CVID cases are sporadic, but there are also families with more than one affected member. A small proportion of patients with CVID present in patterns resembling autosomal recessive or dominant inheritance, and mutations in several genes involved directly or indirectly in B cell differentiation, have been identified. This small subset of CVID patients have defects in inducible co-stimulator (ICOS), CD19, CD20, CD21, CD81, lipopolysaccharide-responsive beige-like anchor (LRBA), B cell-activating factor (BAFF) receptor and CXCR4 [the latter causing WHIM (warts, hypogammaglobulinaemia, infections and myelokathexis) syndrome] [3]. Additionally, two autosomal dominant defects affecting the genes for *NFκB2* and *PIK3CD* have been described recently. The *NFκB2* mutation causes haploinsufficiency and results in a CVID-like phenotype with childhood onset, autoimmune features and adrenal insufficiency [4]. Nuclear factor kappa B2 (NF-κB2) is the principal downstream effector in the non-canonical NF-κB pathway and is required for appropriate B cell development. Dominant gain-of-function mutations in the *PIK3CD* gene encoding the catalytic P110δ and the p85α subunits of phosphoinositide 3-kinase (PI3 kinase) causes hyperactive PI3 kinase signalling, leading to early-onset autoimmunity, recurrent viral infections and bronchiectasis [5,6]. This suggests that clinical trials with PI3 kinase inhibitors are warranted. Most recently, a CVID-like syndrome, characterized by hypogammaglobulinaemia, a progressive loss of circulating B cells, immune dysregulation and lymphocytic infiltration of the brain, lung and gut was recognized to be caused by heterozygous mutations in the *CTLA4* gene [7].

CVID patients can be divided into those who exclusively experience infections (bacterial, viral or opportunistic) and, as a result, often develop chronic lung disease, and a second group who in addition develop an inflammatory condition. In the former subset, where recurrent infections are the primary symptom of concern, affected patients will have a near-normal life expectancy provided that they receive adequate treatment with intravenous immunoglobulin (IVIg) and/or antibiotics. Patients in the inflammatory subset are extremely prone to develop granulomas, autoimmune conditions and malignancies. Granulomas can develop in multiple locations, including the skin, lungs, liver and gut. Autoimmune conditions such as colitis, cytopaenia, hepatitis and malignancies, including leukaemia, lymphoma and colon cancer, are relatively frequent [1]. This subset will generally have a reduced life expectancy and lower quality of life.

Additionally, there is a third group encompassing conditions which are not considered 'classic' CVID: these are defects in T cell development, resulting in a 'CVID-like' condition with early-onset bronchiectasis, autoimmune disease and recurrent viral infections. These conditions (examples are LRBA deficiency [8] and gain-of-function mutations in the P110δ and the p85α subunits of PI3 kinase [5,6]) remain a diagnostic challenge, as it is unclear whether patients are suffering from 'true' CVID or a different type of hypogammaglobulinaemia with secondary B cell deficiency [9].

Because both the genetics and clinical presentation of CVID are so variable, clinical diagnosis usually occurs by a lengthy process of eliminating other disorders. B cell phenotyping, T cell function assays, antigen (including neo-antigen) challenges, lymphokine studies, functional testing to measure processes such as phosphorylation of proteins, flow-based assays for surface and intracellular antigens, enzyme-linked immunosorbent assay (ELISA) and measurement of antibody production following vaccination

with conjugate (Hib and Prevnar) and unconjugated (Pneumovax) vaccines are required to rule out other primary immunodeficiencies (PIDs). Because, in most cases, CVID may not be due to a single gene defect, molecular approaches thus far have been largely unrewarding, and successful in only a minority of CVID patients in identifying a genetic cause.

Patients with a CVID-like phenotype and low numbers of circulating B cells may have mutations in the *BTK* gene, the cause of X-linked agammaglobulinaemia (XLA) or in genes causing autosomal recessive agammaglobulinaemia, including λ5, Igα, Igβ, B cell linker protein (BLINK) and γH [10]. Recently, a homozygous mutation in the p85α subunit of PI3 kinase and a dominant negative mutation in E47 were found to cause agammaglobulinaemia [11,12].

The complexity of the molecular basis of CVID and the heterogeneity of the clinical phenotype requires a carefully designed treatment plan. The primary therapy is infusion of immunoglobulin, which can be either intravenous or subcutaneous, and is dosed based on the patient's immunoglobulin trough levels and clinical response, including frequency of infections. Prophylactic antibiotics help to prevent the development of chronic lung disease and immunosuppressive therapy of autoimmune complications are needed in some patients. Occasionally haematopoietic stem cell transplantation is required. As new causative genetic mutations are identified, new possibilities of gene defect-specific interventions become available. Promising results have been reported from recent studies using rituximab and azathioprine for the treatment of granulomatous lymphocytic interstitial lung disease associated with CVID [13].

In terms of future directions for research into CVID, a key priority is to establish a more comprehensive set of diagnostic criteria for the differentiation of CVID and the less well-defined CVID-like conditions summarized here. Identification of novel CVID biomarkers will help to achieve this goal. Additional work in isolating causative genetic variants by whole exome/genome sequencing provides new opportunities to assist in genetic counselling and more specific therapies. Finally, research into better management of difficult-to-treat CVID symptoms such as subclinical infections, inflammatory complications and GI problems should be undertaken.

Acknowledgements

The author would like to thank Meridian HealthComms Ltd for providing medical writing services.

Disclosures

H. D. O. has received consultancy fees from CSL Behring.

References

1 Resnick ES, Moshier EL, Godbold JH, Cunningham-Rundles C. Morbidity and mortality in common variable immune deficiency over 4 decades. Blood 2012; **119**:1650–7.
2 Jolles S. The variable in common variable immunodeficiency: a disease of complex phenotypes. J Allergy Clin Immunol Pract 2013; **1**:545–56; quiz 57.
3 Salzer U, Warnatz K, Peter HH. Common variable immunodeficiency – an update. Arthritis Res Ther 2012; **14**:223.
4 Chen K, Coonrod EM, Kumanovics A *et al.* Germline mutations in NFKB2 implicate the noncanonical NF-kappaB pathway in the pathogenesis of common variable immunodeficiency. Am J Hum Genet 2013; **93**:812–24.
5 Lucas CL, Kuehn HS, Zhao F *et al.* Dominant-activating germline mutations in the gene encoding the PI(3)K catalytic subunit p110delta result in T cell senescence and human immunodeficiency. Nat Immunol 2014; **15**:88–97.
6 Deau MC, Heurtier L, Frange P *et al.* A human immunodeficiency caused by mutations in the PIK3R1 gene. J Clin Invest 2014; **124**:3923–8.
7 Kuehn HS, Ouyang W, Lo B *et al.* Immune dysregulation in human subjects with heterozygous germline mutations in CTLA4. Science 2014; **345**:1623–7.
8 Lopez-Herrera G, Tampella G, Pan-Hammarstrom Q *et al.* Deleterious mutations in LRBA are associated with a syndrome of immune deficiency and autoimmunity. Am J Hum Genet 2012; **90**:986–1001.
9 Seppanen M, Aghamohammadi A, Rezaei N. Is there a need to redefine the diagnostic criteria for common variable immunodeficiency? Expert Rev Clin Immunol 2014; **10**:1–5.
10 Smith CIE, Conley ME. X-linked agammaglobulinemia and autosomal recessive agammaglobulinemia. In: Ochs HD, Smith CIE, Puck JM, eds. Primary immunodeficiency diseases, a molecular and genetic approach, 3rd edn. New York: Oxford University Press, 2014:299–323.
11 Conley ME, Dobbs AK, Quintana AM *et al.* Agammaglobulinemia and absent B lineage cells in a patient lacking the p85alpha subunit of PI3K. J Exp Med 2012; **209**:463–70.
12 Boisson B, Wang YD, Bosompem A *et al.* A recurrent dominant negative E47 mutation causes agammaglobulinemia and BCR(–) B cells. J Clin Invest 2013; **123**:4781–5.
13 Chase NM, Verbsky JW, Hintermeyer MK *et al.* Use of combination chemotherapy for treatment of granulomatous and lymphocytic interstitial lung disease (GLILD) in patients with common variable immunodeficiency (CVID). J Clin Immunol 2013; **33**:30–9.