Common variable immunodeficiency: a heterogeneous group needs further subclassification

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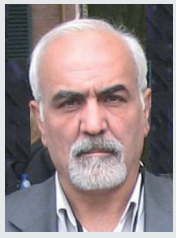

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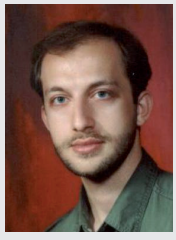

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EXPERT REVIEWS

"Attempts to identify the genes responsible for common variable immunodeficiency have resulted in the discovery of novel monogenic defects during the past few years..."

Common variable immunodeficiency (CVID) is the most common symptomatic primary immunodeficiency disease. It presents clinically as a heterogeneous disorder with recurrent bacterial infections, autoimmune manifestations and lymphoproliferation [1,2]. The diagnostic criteria include immunoglobulin (Ig) levels greater than two standard deviations below the population mean and abnormal antibody responses to protein and/or polysaccharide antigens [3,4]. Patients with CVID are predisposed to chronic and recurrent infections, which mainly occur in the respiratory and GI tracts [2,5]. Early diagnosis and adequate replacement therapy with intravenous Ig reduce the number of infections and improve the patients' quality of life [6,7], while a delay in the diagnosis or inadequate management of CVID may lead to permanent organ damage (e.g., bronchiectasis), morbidity and mortality [8–10]. The exact prevalence of CVID is unknown, although it is estimated to be between 1 in 15,000 and 1 in 117,000, depending on the ethnic background [11].

Despite the occurrence of various abnormalities in both the innate and the adaptive immune systems [12–16], the molecular basis of most cases of CVID remains unknown. Therefore, a diagnosis of CVID is made by the exclusion of other currently known B-cell-failure disorders caused by single gene defects [17–22]. CVID demonstrates many different clinical and immunological features [3,23]. It has been shown that some groups of patients with CVID are particularly susceptible to earlier onset of respiratory diseases and bronchiectasis [24,25], while others display only mild-to-moderate clinical manifestations. In addition, some patients encounter more autoimmune diseases, granulomatous lesions and malignancies. Based on a recent European cohort of 334 CVID patients [3], affected individuals have been divided into distinct clinical phenotypes with different outcomes.

"Early diagnosis and adequate replacement therapy with intravenous Ig reduce the number of infections and improve the patients' quality of life..."

Attempts to identify the genes responsible for CVID have resulted in the discovery of novel monogenic defects during the past few years, including mutations in the inducible costimulator (*ICOS*) gene in T cells [18], transmembrane activator and calcium-modulator and cyclophilin ligand interactor (TACI; encoded by *TNFRSF13B*) [17,19], *CD19* [21] and B-cell-activating factor receptor (BAFF-R; encoded by *TNFRSF13C*) [22] on B cells; as well as a deficiency in MutS homolog 5 (*MSH5*; *Escherichia coli*) [20]. Although these new monogenic defects share clinical phenotypes with CVID, they are actually different entities and may occasionally be misdiagnosed as CVID.

In view of the heterogeneity and diverse nature of CVID, the discovery of a single gene or even single etiology that covers

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all CVID patients is unlikely. The heterogeneity of the clinical symptoms and immunologic defects in CVID might reflect the heterogeneity of the mechanisms leading to the deficiency, and it seems that different genetic defects may account for those CVID patients with distinct clinical features.

The classification of CVID patients to homogenous subpopulations is an essential step required for finding a single gene in the proposed classified groups. During the last few years, various efforts have been made to develop classification systems on the basis of laboratory findings correlated with clinical features to divide CVID patients into more unified subgroups and to help further etiologic research. Early attempts at classifying the disease based on *in vitro* assessments of Ig production have been made, but have not yielded clear clinical correlates [26]. A number of reports have described reduced populations of $CD27^+$ memory B cells and increased percentages of undifferentiated B cells in the peripheral blood of CVID patients [27–29]. These systems have suggested a B-cell classification system that highlights defects at different stages of B-cell differentiation, which correlate with clinical subtypes of CVID. Abnormalities in T-cell numbers and function were the basis of another potential classification scheme [30], with some clinical implications, although its importance remains to be determined in future studies.

There are some recent findings that could characterize a group of CVID patients, including abnormalities in regulatory T cells [31–33], lymphocyte radiosensitivity [34] and functional antibody response to vaccine antigens [24,35]. Although these abnormalities are not sufficient for the universal classification of CVID, they can pave the way for the discovery of more genetic changes underlying the disease.

Although most CVID patients represent sporadic cases without a family history of immunodeficiency, different modes of inheritance, such as autosomal dominant with variable penetrance and autosomal recessive, have been described. The existence of affected family members suggests an autosomal recessive pattern of inheritance in populations with high rates of consanguineous marriages.

> **"The classification of common variable immunodeficiency patients to homogenous subpopulations is an essential step required for finding a single gene in the proposed classified groups."**

Common variable immunodeficiency can occur at any age but has two peaks, in the first and third decades of life [2]. In our experience, pediatric CVID has specific characteristics, such as a more severe course and a high rate of parental consanguinity, which separate it from adult CVID [1,34].

In our opinion, taking together the criteria such as familial presentation, parental consanguinity and presentation with early onset of severe disease will characterize more unified subgroups of patients that will facilitate the identification of potential autosomal recessive defects in CVID.

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