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Chipping away at a mountain: Genomic studies in Common Variable Immunodeficiency

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Abstract

Common variable immunodeficiency (CVID) represents one of the most frequently diagnosed disorders of the immune system. Though several causative and associated genes have been identified, the origins of most cases remain unknown. Diagnostic delay is common due to the gradual evolution and wide spectrum of phenotypes, which can include autoimmune disease, enteropathy, and lung disease. A recent genome wide array identified novel gene associations with CVID, and also showed that identification of a genetic signature via a Support Vector Machine algorithm may be a powerful diagnostic tool. Studies utilizing whole genome or exome sequencing have also met with success in identifying new causes of CVID in subgroups of patients.

Keywords

Immunodeficiency; immunoglobulin; genome

Introduction

Primary immunodeficiency disorders (PIDD) are estimated to affect as many as 1 in 4000 people [1], and over 175 unique diseases have now been described [2]. Greater than 50% of cases of PIDD involve defects in antibody production, and among these, common variable immunodeficiency (CVID) is the most frequent disorder requiring clinical intervention [3]. This disorder is defined by decreased immunoglobulins (IgG and IgM and/or IgA), impaired specific antibody production and recurrent infections. CVID generally requires life-long immunoglobulin replacement to reduce infection rates and improve outcome [4,5]. In addition, CVID is associated with a variety of comorbid conditions, including autoimmune disease, enteropathy, lung disease, and increased risk of malignancies (Table 1) [5,6]. Of note, autoimmune disease has also been associated with other antibody isotype deficiencies [7,8].

CVID has a wide age of onset, with peaks in the first and third decades of life [9]. There is often significant delay in the diagnosis of CVID due to the wide spectrum of phenotypes and

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evolution of laboratory values prior to meeting diagnostic criteria [10]. Cohort studies have demonstrated a significant increase in mortality associated with CVID, due to both infections and non-infectious complications [10,11]. To date, a small number of clinical predictors have been uncovered. Analysis of B-lymphocyte subsets have shown that decreased memory B-cells (CD27+ IgM−) and reduced expression of CD21 correlate with incidence of autoimmune disease [12–14]. However, there are no biomarkers to stratify risk for other complications such as enteropathy or malignancy, which have a profound impact on long-term mortality.

Given its variability in onset and phenotype, CVID has been long suspected to be an "umbrella diagnosis" with likely many underlying etiologies [9]. Familial cases have been described, suggesting rare monogenic causes, though most cases are thought to be polygenic in origin. To date, 10 monogenic causes have been identified, as well as two risk-associated genes [15–22]. Most of these genes encode proteins involved in signaling through the B-cell receptor (CD19, CD21, CD81, PLC-γ2), or proteins involved in co-stimulatory pathways necessary for isotype switching and somatic recombination (ICOS, BAFFR, TACI, MSH5). Of the genes identified, mutations in the transmembrane activator and calcium modulator and cyclophilin ligand interactor (TACI) are most common, being found in 8–10% of CVID cases [23]. However, its role in causation is still unclear, as mutations in TACI occur in many unaffected individuals. The remainder of discovered genes are rare, and thus the cause of nearly 90% of CVID remains unknown.

Genome wide arrays

Recently, the first collaborative genomic-wide array study of CVID sought to look for novel associations with CVID, as well as to address the need for improved diagnostics and prognostic indicators [24]. This study was permitted by the development of the Haplotype Map, a database of over 3 million single nucleotide polymorphisms (SNPs) that occur throughout the human genome at specific frequencies which vary by ethnicity [25]. Unlike genetic sequencing, rare novel mutations would not be uncovered by this method. Analysis of SNPs was paired with determination of copy number variation via the PennCNV Markov model, which allowed detection of deletions and insertions at kilobase resolution [26]. Following analysis of 363 patients and 3031 controls, 8 SNPs were identified with significant over-representation in CVID patients, including polymorphisms in *MHC*, *ADAM28*, *SDK1*, and *UBX10*. Analysis of subphenotypes within CVID patients, including cancer, autoimmune disease, enteropathy among other conditions also correlated with unique SNPs. Assessment of copy number variation showed several significant deletions and duplications, the most notable of which was an intra-exonic duplication in *ORC4L* in 15 patients and none of the controls. *ORC4L* encodes a highly conserved member of the pre-replication complex which is involved in initiation of DNA replication during S-phase [27]. Interestingly, a missense mutation in the same protein has previously been described in association with lymphoproliferative disease [28]. However, there is no known role for ORC4L specific to immunity. Recently, null mutations in *ORC4L* have been described as a cause of Meier-Gorelin syndrome, which is characterized by growth retardation, absent patellae, and microtia [29]. No immunologic phenotype has been described in this disorder.

Perhaps the most striking finding uncovered by Orange *et al.* was the significantly genome-wide burden of copy number variations found in CVID patients, including several with duplications or deletions of greater than 1Mb. As confirmation of germline copy number variation was not performed, it is not clear whether this degree of copy number variation is acquired or inborn. The highly variable age of clinical onset and markedly raised risk of malignancy in CVID resemble diseases of genomic instability. Previous studies have

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demonstrated *in vitro* radiosensitivity in CVID patients [30,31], which further supports this premise.

Finally, through the use of a Support Vector Machine (SVM) algorithm, the authors demonstrated that the unique signature of SNPs and copy number variants could be used successfully for diagnosis of CVID with an overall accuracy of 91% and a positive predictive value of 100%. SVM uses multiple forms of data input to form a linear "hyperplane" which can then be used to predict sample grouping. Though it has found use in many fields, SVM is being used increasingly for biomedical applications [32–34].

Whole genome and exome sequencing

With rapid strides in the accuracy and cost of genomic sequencing, a new approach for exploring familial and subphenotype clusters in CVID has become feasible. Whole genome sequencing was recently used in concert with linkage analysis to identify mutations in PLG-γ2 in patients with CVID, cold urticaria, and autoimmunity [17]. Though extremely powerful, the greatest present limitation of whole genome sequencing lies in its interpretation, as a single individual may have as many as 20,000 single nucleotide variations [35]. Whole exome sequencing reduces this burden of data by limiting sequencing to coding regions, which represent only 1% of the genome but roughly 85% of causative mutations. It is important to note that the present methodology of exon capture has limitations on coverage of the exome, with often upwards of 10% of genes poorly covered or missed altogether [36] Further, polygenic diseases may be. problematic for analysis via sequencing, as multi-pathway disorders could make interpretation of novel mutations extremely challenging. Thus, novel findings must be followed by confirmatory mechanistic biology. Despite these limitations, many studies of CVID utilizing these methods are underway.

Future directions

Genomic studies show great promise in probing the group of disorders that comprise common variable immunodeficiency. The use of a unique "genetic fingerprint" of SNPs and copy number variation could be an extremely powerful diagnostic tool. The use of similar algorithms within CVID subpopulations may also permit risk prediction of comorbid conditions such as autoimmune disease or cancer. Risk stratification would be invaluable in permitting increased screening, diagnosis, and early treatment of these complications. Finally, sequencing of familial clusters may yet reveal novel pathways and therapeutic targets. Targeted sequencing of existing pathways has been used with great success in discovering other forms of primary immunodeficiency, and may be prove to be a valuable strategy in CVID. As technology accelerates, perhaps the task of chipping away at this mountain will become an attainable task.

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Take-home messages

- Common variable immunodeficiency is the most frequently diagnosed form of immunodeficiency requiring clinical intervention, and the cause in 90% of cases is unknown.
- Autoimmune diseases can be a presenting feature of CVID, including autoimmune hemolytic anemia, idiopathic thrombocytopenic purpura, rheumatoid arthritis, inflammatory bowel disease, and granulomatous disease.
- Novel associations between CVID and both single nucleotide polymorphisms and copy number variants have been seen.
- The use of a Support Vector Machine algorithm may permit the genetic fingerprint of CVID to be used diagnostically.
- Genome and exome sequencing are being used successfully to examine familial cases of CVID, though interpretation of single nucleotide variants as well as limitations in genomic coverage remain a challenge.

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Table 1

Non-infectious complications of CVID

Category	Condition	Percentage*
Pulmonary	Chronic lung disease	28%
	Bronchiectasis	11%
Gastrointestinal	Inflammatory bowel disease	20%
	Malabsorption	6%
	Chronic diarrhea	2%
Autoimmune	Idiopathic thrombocytopenic purpura	14%
	Autoimmune hemolytic anemia	7%
	Evan's syndrome	4%
	Rheumatoid arthritis	3%
	Others: neutropenia, pernicious anemia, diabetes mellitus, multiple sclerosis, juvenile idiopathic arthritis, autoimmune thyroiditis, vasculitis, systemic lupus erythematosus	<1%
Granulomatous disease	Lung, liver, lymph nodes, skin	10%
Malignancy	Lymphoid malignancy	8%
	Breast cancer	2%
	Gastric carcinoma	<1%

*From ResnickE. *et al. Blood* (2012) 119: 1650–1657