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# Variable Phenotypic Presentation of Primary Immunodeficiency Diseases: A Challenge for Diagnosis

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## Introduction

Primary Immunodeficiency Diseases (PIDs) are a heterogeneous group of disorders that affect the development or the function of the immune system mostly presenting as severe recurrent infections with an increased incidence of autoimmunity and malignancies. The spectrum of such diseases has grown during the past 50 years, with currently more than 180 different syndromes having been described [1]. In most cases PIDs are monogenic disorders that follow a simple Mendelian inheritance. Some PIDs are particularly common in certain geographical areas because of founder effects, restricted genetic isolates or higher consanguinity rates. Despite major advances over the last 20 years in the molecular characterization of PIDs, many patients still go undiagnosed or are diagnosed late, with adverse clinical consequences and are faced with lifelong disability.

Most of the classical PIDs were identified by their clinical and immunologic presentations and confirmed at their molecular level. However, several immune system gene mutations had variable phenotypic presentations making a firm diagnosis by clinical and immunologic criteria problematic. For example, mutations in Recombinase Activating Gene 1 (RAG1) were found to cause Severe Combined Immunodeficiency Disease (SCID) [2], while hypomorphic mutations in the same gene present with omen syndrome phenotype [3]. It was then found that identical mutations in this gene could cause either syndromes [4] and to make it more complicated hypomorphic mutation in the same gene can present with Oligoclonal γ/δ T cells, autoimmune disease, and CMV infection [5]. Thus, it is possible that environmental or other genetic factors modify the clinical manifestation of such mutations. Several other genes mutations of the immune system result in variable phenotypes. Mutations in Bruton's tyrosine kinase gene (Btk) result into x-linked agammaglobulinemia [6] or polysaccharide antibody deficiency [7]. Mutations in the WASP gene result in Wiskott-Aldrich syndrome but also in X-linked thrombocytopenia [8]. SH2D1A mutations have been shown to cause variously fatal infectious mononucleosis, common variable immunodeficiency [9], or hemophagocytic lymphohistiocytosis [10].

Clinical ambiguity also arises from the fact that identical clinical syndromes can be caused by mutations in different immune system genes. SCID can be caused by at least 14 different genes [11] and more ever Omenn syndrome can be caused by different hypomorphic mutations in SCID causing genes [12]. In addition Hyper IgM syndrome can be caused by mutation in 6 different genes [13]. These variable phenotypic and molecular characterizations of PIDs pose a significant challenge to the approach and the diagnosis mostly related to lack of knowledge, appropriate immunological and molecular assays or the need to screen for several genes.

Several PIDs regional registries already exist in a number of countries. These patient registries have already and will continue to shed light on the pathology and natural history of these varied disorders. Merging these regional registries into larger international databases will help to create a large pool of patient data and the establishment of disease specific database registries will expand our knowledge on variable clinical presentation, management and outcome of the targeted diseases.

Assessment of T Cell Receptor Excision Circles (TRECs) using dried blood spots collected at birth is being used recently for newborn screening of Severe Combined Immunodeficiency (SCID). This assay had the advantage of being quantitative, objective and highly reproducible in addition being able to detect atypical SCIDs and several other T-cell defects [14]. Implementing this newborn screening would be expected to facilitate early diagnosis of such disorders and prevent the long term disability seen secondary to late diagnosis.

These variable phenotypic presentations should alert all physicians who care for patients with recurrent infections that atypical presentations may occur when genes of the immune system are mutated. Extensive molecular work up are needed for patients with atypical presentations otherwise most of these conditions will go undetected, and the full spectrum of phenotypic and genotypic heterogeneity will not be known. One effective global tool for improving diagnosis of PIDs is increasing physician's awareness about these variable phenotypic presentations of PIDs. Continuing education of physicians from different specialties is important including those physicians who treat adolescents and adults. Along with disease-focused awareness campaigns, there is a need to support the development of appropriate diagnostic tools in these areas, including the use of immunological and molecular assays.

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