Results: We generated a phenotype dataset of 1000 individuals with PIDs by annotating the clinical features of these subjects obtained from electronic health records (EHR) with HPO terms. Exome sequencing of these 1000 individuals identified 313 probands with a pathogenic or likely pathogenic (P/LP) variant in a gene associated with the respective clinical presentation. We identified 118 probands where the same gene harbored a P/LP variant in at least three unrelated individuals. We used the clinical and genetic data of 118 individuals in the following areas:

1) We identified P/LP variants in AIRE, PIK3CD, NLRP3, FAS, CTLA4, GATA2, CYBB, STAT1 and TNFRSF13B in at least ten patients that explained their clinical presentations. This dataset allowed us to characterize variable expressivity of diseases associated with these genes by capturing the variability in the observed HPO terms among probands with P/LP variants in the same gene. Dimensional reduction of clinical features of probands allowed us to cluster patients sharing similar phenotypic profiles. We found clinical presentation of individuals with monoallelic P/LP variants in AIRE were relatively less variable and clustered more compactly compared to that of individuals with GATA2 variants.

2) The extent of multiple diagnoses in PID is not well explored. The benchmark cohort we developed allowed us to identify candidates for multiple diagnosis or phenotype expansion by comparing the phenotype profile of each patient expressed in HPO terms to the HPO terms typically observed for a given PID. For example, we identified gain-of-function pathogenic variant in PIK3CD in a patient that explained the clinical features of the PID observed in this patient. However, the patient also displayed developmental delay, congenital hemiplegia, cerebral palsy and absent speech. These features are not known to be associated with PIK3CD variants, making this individual a candidate for >1 genetic diagnoses.

Conclusions: We developed a benchmark dataset where clinical features of patients were described using HPO terms. This dataset allowed us to quantify variable expressivity for certain PID subtypes and to systematically identify potential candidates for multiple diagnosis or phenotypic expansion.

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Two First Cases Of WHIM Syndrome in Ukraine

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Abstract/Case Report Text

Warts, hypogammaglobulinemia, recurrent infections and myelokathexis syndrome is a rare combined immunodeficiency due to autosomal dominant gain-of-function mutations of CXCR4 chemokine receptor. The late diagnosis of WHIM syndrome in two Ukrainian adolescents highlights the diagnostic challenges in this disease.

Patient 1, 12 year-old girl, had recurrent pneumonia since the first year of age; overall she had 7 episodes of pneumonia. She has suffered from chronic bronchitis for last several years. She had recurrent otitis media and chronic pyelonephritis. Neutropenia was revealed when she was 3 year old. During episodes of bacterial infections she occasionally had normal value of neutrophils. The girl does not receive any treatment.

Patient 2, 14 year-old boy, had three episodes of pneumonia when he was 2, 7 and 14 year old. Others symptoms include recurrent herpetic infection, warts on the hands. Since 2 years of age he has haven persistent low neutrophil counts. The child was followed by hematologist and since 5 years of age he has received G-CSF (5 mg/kg) twice a month.

Both children have leukopenia 750 – 1200 cells/mm3, neutropenia – 100 – 300 cells/mm3, lymphopenia 560-830 cells/mm3, low number of B-cells – 30-50 cells/mm3. Hypogammaglobulinemia was not prominent in both children, they have slightly decreased level of IgG (7,1 g/l), normal level of IgM (1,16 – 1,44 g/l), patient 1 has low level of IgA 0,24 g/l. Patient 1 does not have protective level of antibodies to diphtheria and tetanus anatoxin, and anti-Hbs antibodies were absent despite complete immunization.

Bone marrow aspirate revealed hypercellular marrow with granulocytic hyperplasia which was characterized by hypersegmented nuclei and cytoplasmic vacuolization of neutrophils.

On molecular analysis of CXCR4, heterozygous mutation c.1000C>T (p.Arg334*), known as R334X mutation, was detected in both patients, confirming the diagnosis of WHIM syndrome.

Replacement therapy with intravenous immunoglobulin was started in both children together with antibacterial prophylaxis and G-SCF. Vaccination with 4-valent vaccine against HPV infection was recommended for both patients.

WHIM syndrome is very rare immunodeficiency but may be underdiagnosed. The awareness about rare forms primary immunodeficiency is very important in clinical practice for early diagnosis and treatment.

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Practice Survey of the Initial Diagnostic Evaluation of Patients with Suspected Immune-Mediated Cytopenias: A NICER Consortium Study

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