Genetic Testing for Inborn Errors of Immunity Using a Primary Immunodeficiency Panel or a Comprehensive Immune and Cytopenia Panel

Zöe Powis,[1] Kimberly Gall,1 Julie Hathaway,1 Alicia Scocchia,1 Elina Hirvonen,2 Päivi Kokkonen,2 Inka Saarinen,2 Matias Rantanen,2 Pertteli Salmenperä,2 Massimiliano Gentile,2 Jennifer Schleit,1 Lotta Koskinen,2 Jussi Paananen,2 Samuel Myllykangas,2 Juha Koskenvuo2

[1] Blueprint Genetics Inc, Seattle, USA; [2] Blueprint Genetics, Espoo, Finland

Introduction

- Primary immunodeficiencies (PID) are a group of inherited disorders affecting immune system development or function.
- Identifying the genetic etiology significantly impacts patient management but can be challenging if the PID overlaps with hematological disorders like cytopenia and bone marrow failure.
- We developed an NGS panel, the Comprehensive Immune Cytopenia (CIC) Panel, to address this need and compared the results of the panel to those from a Primary Immunodeficiency Panel (PID) during the same period.

Methods

- We reviewed clinical reports from 1,243 consecutive patients with an indication of suspected PIDs who underwent a CIC Panel (642 genes) or the PID Panel (298 genes) at Blueprint Genetics (a CLIA-certified diagnostic laboratory).
- Genetic test results, patient age, clinical information and panel used were extracted from the internal laboratory database.
- Panels included sequence variant, copy number variant (CNV), and targeted analysis of known pathogenic noncoding variants.
- CNV analysis was performed bioinformatically from NGS data using two variant calling algorithms, including a method specific for small, intragenic, exon-level CNVs.
- Difficult to sequence genes are defined as genes complicated by segmental duplication of >90%
- Variant interpretation was performed utilizing American College of Medical Genetics and Genomics (ACMG) guidelines.

Results

- BTK associated agammaglobulinemia (9%) and STAT3 associated Hyper-IgE recurrent infection syndrome (6%) were the most common diagnoses in patients tested with the PID panel.

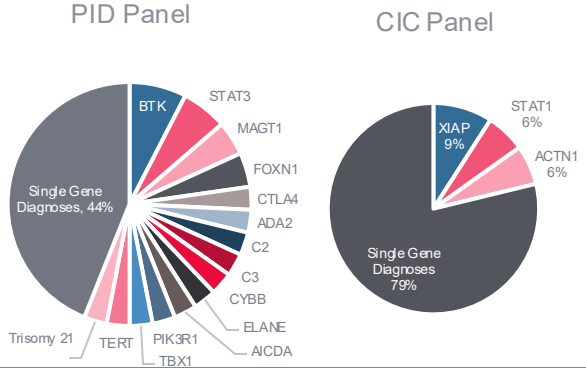
Table 1. Comparison of Primary Immune Deficiency Panel and Comprehensive Immune Cytopenia Panel Results

	Primary Immune Deficiency Panel	Comprehensive Immune and Cytopenia Panel
Number of patients tested	882	361
Median age at testing	14 years	12 years
Percent of cohort 0-18 years	61% (540/882)	69% (241/361)
Percent of cohort >18 years	39% (342/882)	31% (112/361)
Percent diagnoses	7% (66/882)	9% (32/361)
Percent diagnoses due to a copy number variant	16.7% (11/66)	12.5% (4/32)
Percent diagnoses due to an intragenic copy number variant	55% (6/11)	25% (1/4)
Percent diagnoses due to a non-coding variant	11% (6/66)	3% (1/32)
Percent diagnoses in a difficult-to-sequence gene	4.5% (3/66)	19% (6/32)

Results (continued)

- For the patients tested with the CIC Panel, XIAP associated Lymphoproliferative syndrome was the most common diagnosis (9%).
- CNVs were responsible for the diagnosis in 15% of patients while noncoding variants were responsible for the diagnosis in 7% of patients.
- Variants in difficult-to-sequence genes accounted for 10% of the diagnoses.

Figure 1. Diagnoses by panel



Conclusions

- While both panels had a similar diagnostic yield, the most frequent diagnostic genes are panel specific.
- Small and large CNVs, noncoding variants and difficult to sequence genes are important contributors to the diagnostic potential highlighting the value of panels with high-resolution CNV capabilities, methods to resolve difficult to sequence regions, and the inclusion of clinically relevant noncoding variants for this patient population.

Conflict of interest statement: All authors are employed by Blueprint Genetics.

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