The diagnostic yield of next-generation sequencing including non-coding variants and high-resolution copy number variation analysis in the diagnosis of inborn errors of immunity

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Introduction

- Primary immunodeficiencies, or inborn errors of immunity (IEIs), are a group of inherited disorders affecting the immune system.
- Identifying the genetic etiology of an IEI can impact patient management. We report results from over 4,800 patients who underwent multigene panel testing with a clinical indication of an IEI.

Methods

- We examined genetic test results from consecutive patients tested for the indication of IEI in 1 of 11 immunology-related panels. Please scan QR code for details of panels.
- Panel target regions generally included all coding exons, 20 base pairs at intron-exon boundaries, and select clinically relevant non-coding variants. Both sequencing and copy number variation (CNV) analysis was performed.
- Variant interpretation was performed using a point-based modification of the ACMG guidelines.

Results

- Median age at testing of the 4,894 patients was 16 years (range 0-90).
- Pediatric patients (<19 years) accounted for 62% of the cohort. Patients <1 had the highest rate of diagnosis (25%).

Figure 1 Diagnostic rate by panel

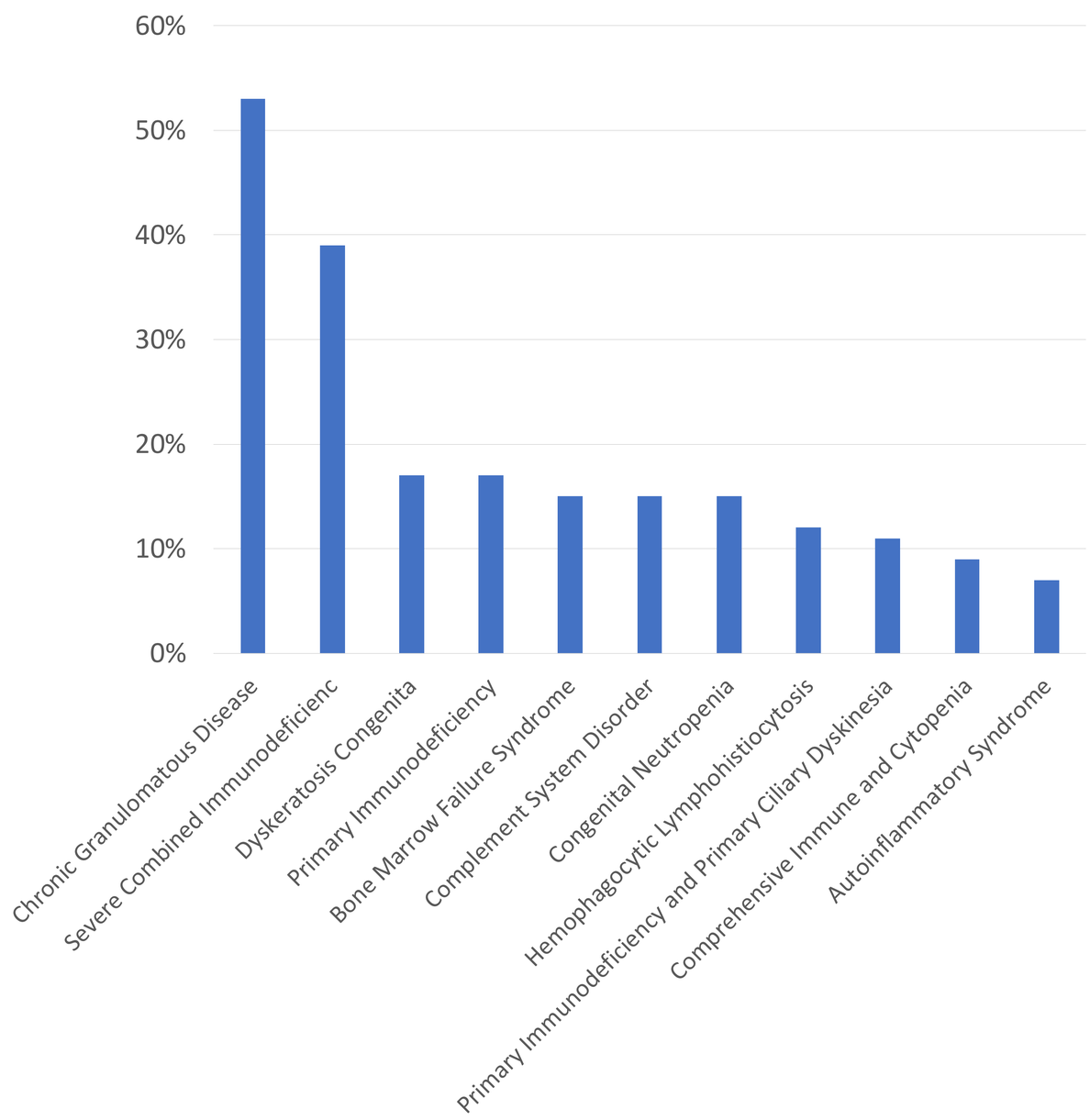

Table 1 Molecular Diagnoses in noncoding variants

Genes	# dx	Genes	# dx
BTK	3	*RMRP*	1
CYBB	1	*RNU4ATAC*	1
IL2RG	1	*TERC*	7
FANCA	2	*TERT*	1
IL2RG	1	*ZAP70*	2
RFXANK	1		

Conclusions

The use of comprehensive panels including detection of small CNVs and non-coding variants are key in the IEI population. They account for over 10% of the diagnostic yield in this large, unselected IEI cohort.

7% of molecular diagnoses were small (<4 exon) **CNVs** and **non-coding** variants

Diagnostic yield was highest in patients **<1 year**

References:

1. Reuter MS, Chaturvedi RR et al. The Cardiac Genome Clinic: implementing genome sequencing in pediatric heart disease. *Genet Med*. 2020;22(6):1015-1024.

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

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