Show me the phenotype: The ordering clinician’s role in genetic variant interpretation for primary immunodeficiency diseases

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BACKGROUND
The rapid pace of new gene discovery and phenotype expansion for Primary Immunodeficiency Diseases (PIDDs) creates challenges for genetic testing and variant interpretation. Whereas well-described clinical case reports in published literature have traditionally served as the source of phenotypic data used for variant interpretation, for PIDDs the causal variants are often private to the patient’s family and thus the sole source of phenotypic information for a novel genetic variant is frequently the history provided by the clinician on the test requisition form. Taking into account such heterogeneous information during variant interpretation requires establishing objective criteria for its inclusion as part of the variant interpretation process.

CLINICAL DATA IN VARIANT INTERPRETATION
- We adapted our laboratory’s pre-existing, evidence-based variant classification framework, called Sherloc (Figure 1) by developing point-based criteria for the inclusion of clinical information such as a patient’s phenotype, familial segregation patterns, and whether the variant is inherited or de novo in the patient.

CASE CRITERIA FOR PIDDs:
- Our case report criteria are derived from expert or consensus guidelines for the clinical diagnoses of PIDDs with modifications for use in the clinical lab setting (Table 2):

CASE EXAMPLES
- Case 1. We received samples from five siblings affected with symptoms of CGD: achromobacter cellulitis, MSSA septicaemia, Burkholderia gladioli infection, adenosine, and abnormal DHR assays (Figure 3). Using the provided clinical information and the CGD criteria outlined in Table 2, we were able to classify the c.1702G>A (p.Glu568Lys) variant in CYBB, which was identified in all siblings tested, as Pathogenic (Table 3).

CLINICAL DATA RESULTS IN MORE ACCURATE VARIANT CLASSIFICATIONS
- Of the 4,057 immunology genetic tests ordered during the studied period, information about the patient’s clinical history was provided in 70% of orders and family history information was provided in 17% of orders.
- Ten variants of uncertain significance were reclassified following receipt of further clinical information or testing of additional relatives.
- In addition, 35 “suspicious” variants of uncertain significance were identified in which one or two additional patient case reports would allow for reclassification from uncertain significance to VUS.
- There were 3,888 variants identified in the 154 genes for which developed case report criteria. Of those, 370 (10%) were classified as well-supported Pathogenic variants.

CONCLUSIONS
- The clinical phenotype and family history data of patients with PIDDs is valuable and necessary for accurate variant interpretation.
- Providing good quality clinical information to the genetic testing laboratory at the time of sample submission is the most efficient way to insure the appropriate interpretation of genetic variants.
- Follow up family studies, laboratory results, and new clinical information can result in the reclassification of variants of uncertain significance to likely pathogenic.


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