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 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. (Figure 1)

The Clinical Observations subcategory of the Sherloc framework is further expanded into the following evidence types (Table 1):

Table 1. Clinical data evidence types utilized in the Sherloc classification system

- To systematically include such phenotypic data for PIDD patients, we defined clinical criteria for 154 PIDD genes.
- We analyzed the clinical information provided from ordering clinicians, and the criteria utilized in the variant interpretation of immunological genetic tests ordered from April 2017 to October 2018.

CASE EXAMPLES

- Case 1. We received samples from five siblings affected with symptoms of CGD: achromobacter cellulitis, MSSA septicaemia, Burkholderia gladioli infection, adenitis, 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).
- Case 2. We received a sample from a 12-year-old female patient with fevers and headaches (Figure 3).
- Two variants in MVK with unknown phase were identified. The clinical information provided was suspicious for MVK but not specific enough to meet case report criteria. Both variants were initially classified as VUS. Following receipt of further clinical information, including mevalonic acid levels and parental samples, we were able to determine the variants were on opposite chromosomes and reclassify both VUSes as Likely Pathogenic.

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 reports, and new clinical information can result in the reclassification of variants of uncertain significance to likely pathogenic.

References:


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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):

Table 2. Examples of case report and pathogenic criteria utilized at Invitae.

- 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.
- There were 3,868 variants identified in the 154 genes for which we developed case report criteria. Of those, 370 (10%) were classified as pathogenic or likely pathogenic (P/LP).

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.

Table 3. Evidence used in classification of E568K variant in CYBB

Table 4. Evidence used in classification of H380R and R277H variants in MVK

Figure 1. Illustration of the Sherloc classification scoring thresholds and evidence categories.

Figure 2. Clinical criteria used in the classification of P/LP variants.

Figure 3. Pedigree from proband in case 1.

Figure 4. Pedigree from proband in case 2.