Paperwork matters! The importance of clinical phenotype information in variant interpretation

Michael Anderson, Carolina Pardo, Hio Chung Kang, Janita Thussberg, Rita Quintana, Karl Erhard, Shu-Huei Wang, Jennifer Holle, Daniela Iacoboni, Ian Wilson, Karen Ouyang

Invitae, San Francisco, CA

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Abstract

The validity and utility of hereditary germline testing require that variant classifications be evidence-based, objective, and systematic. As genetic testing becomes available to a larger percentage of the population, detailed clinical information about patients and their family members becomes increasingly relevant for variant classification. Although sufficient clinical information is often provided in well-described case reports in the published literature, most classified variants are observed only in the clinical testing laboratory setting. Therefore, the ordering clinician becomes the sole source of phenotypic data, as provided on the test requisition form. To objectively incorporate this clinical data into our laboratory’s evidence-based variant classification framework called Sherloc, we defined point-based criteria and usage rules allowing us to evaluate the following: • a patient’s clinical phenotype • variant segregation in families • variant de novo status

As part of this process, we developed a set of predefined clinical criteria for 130 oncology genes. For genes such as NF2 and STK11, our interpretation criteria are nearly identical to the consensus clinical diagnostic criteria. For genes that lack a formal consensus, such as SDHB, we took a rigorous, conservative approach in establishing internal criteria that considers age of onset, phenotypic specificity, penetrance, prevalence, and the existence of phenocopies. The application of our method is illustrated in cases of STK11 and SDHB variants, in which detailed phenotypic information provided by the clinician impacts variant classification. These results highlight the need for ordering providers to share detailed clinical patient information, as it may influence variant classification and ultimately, clinical care.

Sherloc clinical evidence

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

Among the five main evidence categories in Sherloc (Figure 1), the Clinical Observations category (위) contains evidence types related to case report criteria (i.e., compelling phenotypic presentations in a tested individual), co-segregation of the variant within a single family or multiple unrelated families, and de novo events (Table 1). Each evidence type has been further expanded to two to three sub-evidence types, allowing for the additive nature of evidence towards classifying a variant as pathogenic (5 pathogenic points).1

Table 1. Sherloc case reports, segregation, and de novo evidence types.

Table 2. Pathogenic evidence for the STK11 variant, c.526G>A (p.Asp176Asn).

Our case report criteria often mimic consensus diagnostic/testing criteria

Like NF2, our case report criteria are very similar to the consensus diagnostic or testing criteria for: BLM, BMPR1A, CDCT3, CDKN1B, DNM2, DDR2, FBXW7, FLCN, KIT, MEN1, NFI, PDCD10, PTEN, RB1, RET, SMAD4, STK11, TP53, TSC1, TSC2, VHL, and genes associated with Diamond-Blackfan anemia, Fanconi anemia, and Lynch syndrome.

Developing case report criteria in the absence of consensus diagnostic criteria

For SDHB, which lacks formal consensus criteria, we established internal criteria based on prevalence, penetrance, age of onset, specificity of the phenotype, and known phenocopies for causing pheochromocytoma (PCC) and/or paraganglioma (PGL) (Table 3, Figure 5).

Table 3. Clinical data considered in developing the SDHB case report criteria.12

Phenocopies such as SDHA, SDHAQ2, SDHC, SDHD, MAX, TMEM127, RET, NFI, and VHL should be tested.

In the case of the SDHB variant, c.2935G>A (p.Cys88Tyr), the clinical data is highly suggestive of the variant being disease causing. However, further information is needed before making that assertion (Table 4).

Table 4. Pathogenic evidence for the SDHB variant, c.2935G>A (p.Cys88Tyr).

Detailed clinical information leads to more accurate variant classifications

We received a sample from a 29-year-old individual with mucocutaneous macules and history of hamartomatous polyps. Her two children also had mucocutaneous macules and multiple paternal aunts and uncles reportedly had cancers associated with Peutz-Jeghers syndrome (PJS). Multigene panel testing revealed the STK11 variant, c.526G>A (p.Asp176Asn).

Applying our case report criteria to this patient increased the total number of case reports to 3 (including two families identified in peer-reviewed publications).3,4 For this STK11 variant, its pathogenic classification results principally from the detailed clinical phenotypic information available, and the use of case reports and segregation evidence (Figures 3 and 4, Table 2).

Table 2. Pathogenic evidence for the STK11 variant, c.526G>A (p.Asp176Asn).

Figure 2. Invitae NF2 case report criteria.

Figure 3. Invitae STK11 case report criteria.

Figure 4. Pedigree illustrating our internal STK11 patient case.

References