“Phenotypes of Distinction”: When and how to integrate unique phenotypic information into variant interpretation


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Introduction

A common error made in the course of sequence variant classification is to conclude incorrectly that a novel VUS found in a patient with a disease must be causative. This incorrect conclusion arises from an overestimate of the prior probability that any variants found in a gene associated with the patient’s disorder must be causative. In fact, the likelihood that any variants detected in a gene cause disease depends on how distinctive the phenotype of the individual is, the degree of locus heterogeneity, and the fraction of locus heterogeneity that is accounted for by the genes being tested, and the prevalence of phenocopies in the population. The likelihood is also modulated by the observed genotype in the patient. The ACMG Interpretation of Sequence Variants guidelines address this subject with a single, somewhat vague criterion: PP4, “Patient’s phenotype or family history is highly specific for a disease with a single genetic etiology.” Because the presence of a distinctive phenotype in a patient can provide a powerful line of evidence for variant classification, we set out to establish a systematic approach for integrating unique phenotypic data into variant interpretation with more detailed, gene-level guidelines. For well-described hereditary diseases with a specific phenotype, there is a relatively high prior probability that pathogenic variants (s) will be detected, if the appropriate genes have been sequenced.

Methods

- We use a point system for variant interpretation that is based on the ACMG guidelines.

- We defined a new set of evidence-based criteria that can be applied during variant interpretation when the criteria are met: (1) our diagnostic yield is >75% for the gene(s) tested, (2) the clinical features described in a given patient (literature or Invitae patient) must be specific and they are essentially pathognomonic for the disorder, and (3) the patient’s genotype must match the expected inheritance of the disease. The relative weight of the criteria is determined by the likelihood that a patient’s observed genotype explains disease:

<table>
<thead>
<tr>
<th>Inheritance</th>
<th>Path Points</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>AR, XR</td>
<td>2</td>
<td>Homozygous or hemizygous variant in pathognomonic gene</td>
</tr>
<tr>
<td>AR, XR</td>
<td>1.5</td>
<td>Rare het variant co-occurring w/ LP/P variant in pathognomonic gene</td>
</tr>
<tr>
<td>AR, XR</td>
<td>1</td>
<td>Rare het variant co-occurring w/ another rare het variant in pathognomonic gene</td>
</tr>
</tbody>
</table>

- To use this criteria, we first pre-curate information on our diagnostic yield of the test given the genes tested and the unique features of the disorder which must be present. An example is shown below:

<table>
<thead>
<tr>
<th>Test</th>
<th>Genes</th>
<th>Diagnostic yield for the defined disorder (must be &gt;75%)</th>
<th>Diagnostic Criteria (aka Minimum REQUIRED features)</th>
<th>Reference</th>
</tr>
</thead>
<tbody>
<tr>
<td>AR</td>
<td>X-linked L1 syndrome</td>
<td>85% if criteria are met</td>
<td>1 affected family member affected + L1 syndrome (2 of 4 features below)AND</td>
<td>PMID: 3664249</td>
</tr>
<tr>
<td>AR</td>
<td>X-linked L1 syndrome</td>
<td>50% if criteria are met</td>
<td>1 affected family member affected + L1 syndrome (2 of 4 features below)</td>
<td>PMID: 3664249</td>
</tr>
</tbody>
</table>

Results

- As of September 16, 2016, we have used this criteria to aid in the interpretation of 84 samples (77 unique variants)

- As a result of these new criteria, we have been able to classify 30 unique rare variants as likely pathogenic or pathogenic

- In 42 instances, these criteria were applied for variant interpretation and the variant remained a VUS. However, the use of these criteria make it easier to get to LP/P in the future via family variant testing and/or additional cases.

- 21 patients have received a positive genotypic diagnosis for primary ciliary dyskinesia, L1 syndrome, pyruvate responsive epilepsy, DHPR deficiency, MACD deficiency, and SCID - they would have received uncertain findings without the use of these criteria.

Conclusions

- We have developed a systematic framework for the inclusion of highly distinctive phenotypic information when performing variant analysis.

- Careful curation of the disorders for which these criteria can be used is necessary, including the required distinctive phenotypes along with the diagnostic yield for testing individuals with the distinctive phenotypes.

- Each of the new evidence types on their own are insufficient to reach a likely pathogenic interpretation if the variant has only been seen in 1 affected individual; population frequencies, functional studies, and other clinical findings are necessary to reach a likely pathogenic classification.

- This framework provides a mechanism to account for the increased prior probabilities for testing in rare disorders with highly distinctive phenotypes.


References

1. PMID: 25741868