CENTER FOR INDIVIDUALIZED MEDICINE

Clinical Variant Interpretation Lab
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Annotation (3ry Analysis)  
ACMG Guidelines Framework  
Variant Interpretation Lab Exercise
Objectives:

- Overview of challenges and examples of automated and manual variant interpretation.
- Franklin does give a preliminary classification, however, students will review and verify each criteria/question discussed in class.
# Variant Interpretation Framework Summary

<table>
<thead>
<tr>
<th>Concept</th>
<th>Questions</th>
<th>ACMG Criteria</th>
<th>Resources</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Allele Frequency</strong></td>
<td>(1) Common or rare?</td>
<td>BA1, BS1, PM2</td>
<td>gnomAD</td>
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<td></td>
<td>(2) Variant Impact/Type</td>
<td></td>
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<td></td>
<td>Loss of function In-frame indel</td>
<td>PVS1</td>
<td>VEP, UCSC web browser</td>
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<tr>
<td><strong>Computational &amp; Predictive Data</strong></td>
<td>(3) In-silico predictions?</td>
<td>PP3, BP4</td>
<td>Franklin summary</td>
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<td></td>
<td>Potential splicing impact?</td>
<td></td>
<td>Special attention to:</td>
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<tr>
<td></td>
<td></td>
<td>BP7</td>
<td>SpliceAI, REVEL (&gt;0.7)</td>
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<tr>
<td></td>
<td>(4) Constraint metrics</td>
<td>PP2, BP1</td>
<td></td>
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<tr>
<td></td>
<td>Gene/regional level</td>
<td></td>
<td>gnomAD</td>
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<tr>
<td><strong>Functional Knowledge</strong></td>
<td>(5) Residue/Domain? Hotspot?</td>
<td>PM1</td>
<td>Uniprot, ClinVar, HGMD</td>
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<td></td>
<td>(6) Variant effect functionally studied?</td>
<td>PS3, BS3</td>
<td>ClinVar, HGMD, Pubmed</td>
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<tr>
<td><strong>Clinical Knowledge</strong></td>
<td>(7) Interpretation Databases - ClinVar</td>
<td>PP5, PM5, PS1</td>
<td>ClinVar, HGMD, Pubmed</td>
</tr>
<tr>
<td>(published, or case/sample specific)</td>
<td>(8) Previously reported cases?</td>
<td>PS4, BS2, BP5</td>
<td>Direct Google Search</td>
</tr>
<tr>
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<td>(9) Phenotype specificity</td>
<td>PP4</td>
<td></td>
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<td></td>
<td>(10) Segregation? De novo?</td>
<td>PP1, BS4, PS2, PM6</td>
<td>Some of these criteria are also specific to the clinical details of individual carrying the variant</td>
</tr>
<tr>
<td></td>
<td>(11) Trans / cis observations</td>
<td>PM3, BP2</td>
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FRANKLIN OVERVIEW

https://franklin.genoox.com/clinical-db/home
Please review the classification for the following variant/case:

**Case 1 Information:**

- 22yo female underwent genetic testing for hereditary cancer predisposition.
- Patient was referred to clinical genomics because of strong family history of early onset breast and ovarian cancer (<45yo age of onset in mother, 2 maternal aunts and a cousin)

**Variant Identified:**

BRCA2  
(NM_000059)  
c.2979G>A  
p.Trp993*  
Heterozygous state

**Genomic DNA (hg19):**  
Chr13(GRCh37):g.32911471G>A
Please review the classification for the following variant/case:

Case 2 Information:

- 30yo lawyer submitted his sample for state-funded project evaluating the effects
- Patient is alive and healthy. No self-reported history of hypercholesterolemia or any genetic disorder.

Variant Identified:

**LDLR**
(NM_000527.5)
c.1784G>A
p.Arg595Gln
Heterozygous state

**Genomic DNA (hg19):**
Chr19(GRCh37):g.11227613G>A
Please review the classification for the following variant/case:

Case 3 Information:

- 30yo patient with no family history underwent a predisposition screen assay with a clinical reference company.

- No other information available.

Variant Identified:

PMS2
(NM_000535):
c.989-1G>T
p.?
Heterozygous state

Genomic DNA (hg19):
Chr7(GRCh37):g.6029587C>A