Perspectives on Existing Genetic Variation Resources: A Researcher’s Perspective

Leslie G. Biesecker, M.D.
Chief, Genetic Disease Research Branch
NHGRI
Primary Variant

Proband

Whole genome/exome

X number of variants

Variants of interest

Gene Discovery
572 Probands
Whole genome/exome
X number of variants
Variant of interest
Secondary Variants
181,742
Gene Discovery
CS Secondary Variant

572 Probands

Whole exome

X number of variants

Secondary Variants (nonsense, nonsynonymous, frameshift, splice) 181,742

Variant of interest

37 Adult onset cancer susceptibility genes 455 variants

Gene Discovery
Framework for Variant Interpretation

Quality

\[ \text{MPG} > 10 \]
\[ \text{MPG/coverage} < 0.5 \]
\[ \text{ClinSeq} \geq ? \]
\[ \text{dbSNP MAF} \geq ? \]
\[ 1000 \text{ genomes} \]
\[ \text{Candidate} \]

\[ \text{HGMD and/or LSDB pathogenicity data} \]

- stop
- VUS
- confirm pathogenicity and report
- reevaluate quarterly

If HGMD and/or LSDB pathogenicity data is negative: stop

If HGMD and/or LSDB pathogenicity data is positive: confirm pathogenicity and report

If HGMD and/or LSDB pathogenicity data is uncertain: reevaluate quarterly
Framework for Variant Interpretation

[Flowchart diagram showing decision criteria for variant interpretation.]

- **Frequency**
  - \( \text{MPG} > 10 \)
  - \( \text{MPG/coverage} < 0.5 \)
  - \( \text{dbSNP MAF} \geq ? \)
  - \( \text{ClinSeq} \geq ? \)
  - Candidate

- **HGMD and/or LSDB pathogenicity data**
  - -
  - +
  - stop
  - ?
  - VUS
  - reevaluate quarterly
  - confirm pathogenicity and report
ClinSeq™ Cancer Variant Filtering

- Frequency
  - MPG > 10
    - yes
    - stop
  - no
    - MPG/coverage < 0.5
      - yes
      - stop
    - no
      - ClinSeq ≥ 1%
        - yes
        - stop
        - only include individuals in denominator with MPG/coverage ≥ 0.5
      - no
        - dbSNP MAF ≥ 0.015
          - yes
          - stop
        - no
          - Candidate
  - stop

- HGMD and/or LSDB pathogenicity data
  - -
    - stop
  - +
    - VUS
      - reevaluate quarterly
    - confirm pathogenicity and report
ClinSeq™ Cancer Variant Filtering

Frequency

- MPG>10
  - yes
  - no
  - MPG/coverage < 0.5
    - yes
    - stop
    - no
    - ClinSeq ≥ 1%
      - yes
      - stop
      - no
      - dbSNP MAF ≥ 0.015
        - yes
        - stop
        - no
        - Candidate
          - HGMD and/or LSDB pathogenicity data
            - -
              - - stop
              - ? VUS
                - - reevaluate quarterly
                - + confirm pathogenicity and report

- 451
  - 430
  - 334
Evaluation of Candidates

- Controls
- Multiple reports
- Functional data
- Presence with other causative mutations
- Segregation with disease (LD & linkage caveat)
- De novo (assuming parentage)
- Penetrance
- Phenocopies
## VarSifter - HGMD

<table>
<thead>
<tr>
<th>Chr</th>
<th>LeftFlank</th>
<th>RightFlank</th>
<th>Gene_name</th>
<th>HGMDids</th>
<th>HGMDdisease</th>
<th>HCMDtags</th>
<th>HGMDinGene</th>
<th>transcript</th>
</tr>
</thead>
<tbody>
<tr>
<td>chr13</td>
<td>31810006</td>
<td>31810008</td>
<td>BRCA2</td>
<td>CM050182</td>
<td>Breast cancer ?</td>
<td>DM</td>
<td>y</td>
<td>uc001uub.1</td>
</tr>
<tr>
<td>chr13</td>
<td>31810053</td>
<td>31810055</td>
<td>BRCA2</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>y</td>
<td>uc001uub.1</td>
</tr>
<tr>
<td>chr13</td>
<td>31810072</td>
<td>31810074</td>
<td>BRCA2</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>y</td>
<td>uc001uub.1</td>
</tr>
<tr>
<td>chr13</td>
<td>31810749</td>
<td>31810751</td>
<td>BRCA2</td>
<td>CM003133</td>
<td>Breast and/or ovarian cancer ?</td>
<td>DM</td>
<td>y</td>
<td>uc001uub.1</td>
</tr>
<tr>
<td>chr13</td>
<td>31811084</td>
<td>31811086</td>
<td>BRCA2</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>y</td>
<td>uc001uub.1</td>
</tr>
<tr>
<td>chr13</td>
<td>31811270</td>
<td>31811272</td>
<td>BRCA2</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>y</td>
<td>uc001uub.1</td>
</tr>
<tr>
<td>chr13</td>
<td>31811689</td>
<td>31811691</td>
<td>BRCA2</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>y</td>
<td>uc001uub.1</td>
</tr>
<tr>
<td>chr13</td>
<td>31811803</td>
<td>31811805</td>
<td>BRCA2</td>
<td>CM041731</td>
<td>Breast and/or ovarian cancer ?</td>
<td>DM</td>
<td>y</td>
<td>uc001uub.1</td>
</tr>
<tr>
<td>chr13</td>
<td>31811970</td>
<td>31811979</td>
<td>BRCA2</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>y</td>
<td>uc001uub.1</td>
</tr>
<tr>
<td>chr13</td>
<td>31812043</td>
<td>31812045</td>
<td>BRCA2</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>y</td>
<td>uc001uub.1</td>
</tr>
<tr>
<td>chr13</td>
<td>31812045</td>
<td>31812047</td>
<td>BRCA2</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>y</td>
<td>uc001uub.1</td>
</tr>
<tr>
<td>chr13</td>
<td>31812223</td>
<td>31812225</td>
<td>BRCA2</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>y</td>
<td>uc001uub.1</td>
</tr>
<tr>
<td>chr13</td>
<td>31812235</td>
<td>31812237</td>
<td>BRCA2</td>
<td>CM010170</td>
<td>Breast cancer ?</td>
<td>DM</td>
<td>y</td>
<td>uc001uub.1</td>
</tr>
<tr>
<td>chr13</td>
<td>31812437</td>
<td>31812439</td>
<td>BRCA2</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>y</td>
<td>uc001uub.1</td>
</tr>
<tr>
<td>chr13</td>
<td>31812591</td>
<td>31812593</td>
<td>BRCA2</td>
<td>CM994286</td>
<td>Breast and/or ovarian cancer ?</td>
<td>DM</td>
<td>y</td>
<td>uc001uub.1</td>
</tr>
<tr>
<td>chr13</td>
<td>31812813</td>
<td>31812815</td>
<td>BRCA2</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>y</td>
<td>uc001uub.1</td>
</tr>
<tr>
<td>chr13</td>
<td>31812816</td>
<td>31812818</td>
<td>BRCA2</td>
<td>CM043917</td>
<td>Breast cancer ?</td>
<td>DM</td>
<td>y</td>
<td>uc001uub.1</td>
</tr>
<tr>
<td>chr13</td>
<td>31812829</td>
<td>31812831</td>
<td>BRCA2</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>y</td>
<td>uc001uub.1</td>
</tr>
<tr>
<td>chr13</td>
<td>31812838</td>
<td>31812840</td>
<td>BRCA2</td>
<td>CM022331</td>
<td>Breast and/or ovarian cancer</td>
<td>DM</td>
<td>y</td>
<td>uc001uub.1</td>
</tr>
<tr>
<td>chr13</td>
<td>31816705</td>
<td>31816707</td>
<td>BRCA2</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>y</td>
<td>uc001uub.1</td>
</tr>
<tr>
<td>chr13</td>
<td>31827308</td>
<td>31827310</td>
<td>BRCA2</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>y</td>
<td>uc001uub.1</td>
</tr>
<tr>
<td>chr13</td>
<td>31827386</td>
<td>31827388</td>
<td>BRCA2</td>
<td>CM960194</td>
<td>Breast cancer</td>
<td>DM</td>
<td>y</td>
<td>uc001uub.1</td>
</tr>
<tr>
<td>chr13</td>
<td>31828632</td>
<td>31828634</td>
<td>BRCA2</td>
<td>CM012590</td>
<td>Breast and/or ovarian cancer</td>
<td>DM</td>
<td>y</td>
<td>uc001uub.1</td>
</tr>
<tr>
<td>chr13</td>
<td>31828672</td>
<td>31828674</td>
<td>BRCA2</td>
<td>CM994287</td>
<td>Breast and/or ovarian cancer ?</td>
<td>DM</td>
<td>y</td>
<td>uc001uub.1</td>
</tr>
<tr>
<td>chr13</td>
<td>31835487</td>
<td>31835489</td>
<td>BRCA2</td>
<td>CM043984</td>
<td>Breast and/or ovarian cancer</td>
<td>DM</td>
<td>y</td>
<td>uc001uub.1</td>
</tr>
<tr>
<td>chr13</td>
<td>31835520</td>
<td>31835522</td>
<td>BRCA2</td>
<td>CM042715</td>
<td>Breast cancer</td>
<td>DM</td>
<td>y</td>
<td>uc001uub.1</td>
</tr>
</tbody>
</table>
Screening for BRCA1, BRCA2, CHEK2, PALB2, BRIP1, RAD50, and CDH1 mutations in high-risk Finnish BRCA1/2 founder mutation-negative breast and/or ovarian cancer individuals.

Kuutonen KM, Rekhni A, Vihinen M, Schleutker J, Sallinen SL.
Department of Pediatrics, Genetics Outpatient Clinic, Tampere University Hospital, Biokatu 6, Tampere, 33520, Finland. Satu-Leena.Sallinen@phpp.fi

Abstract

INTRODUCTION: Two major high-penetration breast cancer genes, BRCA1 and BRCA2, are responsible for approximately 20% of hereditary breast cancer (HBC) cases in Finland. Additionally, rare mutations in several other genes that interact with BRCA1 and BRCA2 increase the risk of HBC. Still, a majority of HBC cases remain unexplained which is challenging for genetic counseling. We aimed to analyze additional mutations in HBC-associated genes and to define the sensitivity of our current BRCA1/2 mutation analysis protocol used in genetic counseling.

METHODS: Eighty-two well-characterized, high-risk hereditary breast and/or ovarian cancer (HBOC) BRCA1/2-founder mutation-negative Finnish individuals, were screened for germline alterations in seven breast cancer susceptibility genes, BRCA1, BRCA2, CHEK2, PALB2, BRIP1, RAD50, and CDH1. BRCA1/2 were analyzed by multiplex ligation-dependent probe amplification (MLPA) and direct sequencing. CHEK2 was analyzed by the high resolution melt (HRM) method and PALB2, RAD50, BRIP1 and CDH1 were analyzed by direct sequencing. Carrier frequencies between 82 (HBOC) BRCA1/2-founder mutation-negative Finnish individuals and 384 healthy Finnish population controls were compared by using Fisher's exact test. In silico prediction for novel missense variants effects was carried out by using Pathogenic-Or-Not-Pipeline (PON-P).

RESULTS: Three previously reported breast cancer-associated variants, BRCA1 c.5096C > T, CHEK2 c.470T > C, and CHEK2 c.1100delC, were observed in eleven (13.4%) individuals. Ten of these individuals (12.2%) had CHEK2 variants, c.470T > C and/or c.1100delC. Fourteen novel sequence alterations and nine individuals with more than one non-synonymous variant were identified. One of the novel variants, BRCA2 c.72A > T (Leu24Phe) was predicted to be likely pathogenic in silico. No large genomic rearrangements were detected in BRCA1/2 by multiplex ligation-dependent probe amplification (MLPA).

CONCLUSIONS: In this study, mutations in previously known breast cancer susceptibility genes can explain 13.4% of the analyzed high-risk BRCA1/2-negative HBOC individuals. CHEK2 mutations, c.470T > C and c.1100delC, make a considerable contribution (12.2%) to these high-risk individuals but further segregation analysis is needed to evaluate the clinical significance of these mutations before applying them in clinical use. Additionally, we identified novel variants that warrant additional studies. Our current genetic testing protocol for 28 Finnish BRCA1/2-founder mutations and protein truncation test (PTT) of the largest exons is sensitive enough for clinical use as a primary screening tool.

PMID: 21356067 [PubMed - as supplied by publisher] PMCID: PMC3109580 Free PMC Article
**Locus-Specific Databases**

**Locus Specific Database list**
Based on various online resources and direct submissions of LSDBs

**Locus Specific Mutation Databases**

IMPORTANT NOTE: Genes are in order of HUGO APPROVED GENE DESIGNATION, not alias. e.g. "p53" will be found under "TP53" while "CD40L" or "TNFSF5" will be found under "CD40LG" and so on.

If you wish to add a gene you can do so here.

Please select the first letter of the Gene:

A B C D E F G H I J K L M N O P Q R S T U V W X Y Z

Or, specify the HGNC Gene Symbol:

Go to this gene »

397 public entries

<table>
<thead>
<tr>
<th>Gene Symbol</th>
<th>Database</th>
<th>Curators</th>
<th>Software</th>
</tr>
</thead>
<tbody>
<tr>
<td>AARS</td>
<td>LOVD - Leiden Open Variation Database <a href="https://grenada.lumc.nl/LOVD2/shared1/home.php?select_db=AARS">Link</a></td>
<td>Curator Vacancy</td>
<td>Leiden University Medical Center</td>
</tr>
</tbody>
</table>

**Related Links:**

- [http://www.hgvs.org/dblist/glsdb.html](http://www.hgvs.org/dblist/glsdb.html)
### LOVD - Variant listings

<table>
<thead>
<tr>
<th>Path</th>
<th>Codon_nr</th>
<th>DNA_change</th>
<th>DNA_reported</th>
<th>RNA_change</th>
<th>Protein</th>
<th>Type</th>
<th>Cons_predicted</th>
<th>DB-ID</th>
<th>Variant Remarks</th>
<th>Origin</th>
<th>Variant reference</th>
</tr>
</thead>
<tbody>
<tr>
<td>+/-</td>
<td>00</td>
<td>c.7C&gt;G</td>
<td>-47306C&gt;G (5' of ATG)</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>APC_00415</td>
<td>numbering 5' of ATG</td>
<td>-</td>
<td>-</td>
<td></td>
</tr>
<tr>
<td>+/-</td>
<td>00</td>
<td>c.7C&gt;T</td>
<td>-47287C&gt;T</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>APC_00416</td>
<td>numbering 5' of ATG</td>
<td>-</td>
<td>-</td>
<td></td>
</tr>
<tr>
<td>+/-</td>
<td>00</td>
<td>c.7insG</td>
<td>-47307insG</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>APC_00417</td>
<td>numbering 5' of ATG</td>
<td>-</td>
<td>-</td>
<td></td>
</tr>
<tr>
<td>+/-</td>
<td>00</td>
<td>c.7T&gt;G</td>
<td>-47481T&gt;G</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>APC_00418</td>
<td>numbering 5' of ATG</td>
<td>-</td>
<td>-</td>
<td></td>
</tr>
<tr>
<td>+/-</td>
<td>01_15+promoter</td>
<td>del</td>
<td>cytogeneticdeletion</td>
<td>-</td>
<td>-</td>
<td>deletion, large</td>
<td>deletion, large</td>
<td>APC_00200</td>
<td>cytogenetic deletion</td>
<td>unknown</td>
<td>Raelle et al. 2001</td>
</tr>
<tr>
<td>+/-</td>
<td>01_15+promoter</td>
<td>del</td>
<td>cytogeneticdeletion</td>
<td>-</td>
<td>-</td>
<td>deletion, large</td>
<td>deletion, large</td>
<td>APC_00200</td>
<td>cytogenetic deletion</td>
<td>de novo</td>
<td>Aretz et al. 2005</td>
</tr>
<tr>
<td>+/-</td>
<td>01_15+promoter</td>
<td>del</td>
<td>cytogeneticdeletion</td>
<td>-</td>
<td>-</td>
<td>deletion, large</td>
<td>deletion, large</td>
<td>APC_00200</td>
<td>cytogenetic deletion</td>
<td>de novo</td>
<td>Aretz et al. 2005</td>
</tr>
<tr>
<td>+/-</td>
<td>01_15+promoter</td>
<td>del</td>
<td>cytogeneticdeletion</td>
<td>-</td>
<td>-</td>
<td>deletion, large</td>
<td>deletion, large</td>
<td>APC_00200</td>
<td>cytogenetic deletion</td>
<td>unknown</td>
<td>Aretz and Friedl (unpublished)</td>
</tr>
<tr>
<td>+/-</td>
<td>01</td>
<td>c.70C&gt;T</td>
<td>-</td>
<td>-</td>
<td>p.Arg24X</td>
<td>substitution, base pair</td>
<td>nonsense</td>
<td>APC_00551</td>
<td>-</td>
<td>-</td>
<td></td>
</tr>
<tr>
<td>+/-</td>
<td>01_15</td>
<td>del</td>
<td>g.26940-?_133343+del</td>
<td>-</td>
<td>-</td>
<td>deletion, large</td>
<td>deletion, large</td>
<td>APC_00587</td>
<td>-</td>
<td>familial</td>
<td>Kanning-Snojel et al. 2008</td>
</tr>
<tr>
<td>+/-</td>
<td>01+promoter</td>
<td>del</td>
<td>g.35041-?_52505+del</td>
<td>-</td>
<td>-</td>
<td>deletion, large</td>
<td>deletion, large</td>
<td>APC_00526</td>
<td>-</td>
<td>familial</td>
<td>Aretz et al. 2005</td>
</tr>
<tr>
<td>+/-</td>
<td>01+promoter</td>
<td>del</td>
<td>g.35041-?_52505+del</td>
<td>-</td>
<td>-</td>
<td>deletion, large</td>
<td>deletion, large</td>
<td>APC_00526</td>
<td>-</td>
<td>familial</td>
<td>Aretz et al. 2005</td>
</tr>
<tr>
<td>+/-</td>
<td>01+promoter</td>
<td>del</td>
<td>g.35041-?_52505+del</td>
<td>-</td>
<td>-</td>
<td>deletion, large</td>
<td>deletion, large</td>
<td>APC_00526</td>
<td>-</td>
<td>familial</td>
<td>Aretz et al. 2005</td>
</tr>
<tr>
<td>+/-</td>
<td>01_05+promoter</td>
<td>del</td>
<td>g.35041-7_78383+7</td>
<td>-</td>
<td>-</td>
<td>deletion, large</td>
<td>deletion, large</td>
<td>APC_00527</td>
<td>-</td>
<td>familial</td>
<td>Aretz et al. 2005</td>
</tr>
<tr>
<td>Path</td>
<td>Exon</td>
<td>Codon_nr</td>
<td>DNA change</td>
<td>DNA_reported</td>
<td>RNA change</td>
<td>Protein</td>
<td>Type</td>
<td>Cons_predicted</td>
<td>DB-ID</td>
<td>Variant remarks</td>
<td>Origin</td>
</tr>
<tr>
<td>------</td>
<td>------</td>
<td>----------</td>
<td>---------------</td>
<td>--------------</td>
<td>------------</td>
<td>-------------</td>
<td>-----------------</td>
<td>----------------</td>
<td>-------</td>
<td>-----------------</td>
<td>--------</td>
</tr>
<tr>
<td>-?</td>
<td>00</td>
<td>-</td>
<td>c.7C&gt;G</td>
<td>-</td>
<td>-</td>
<td>deletion</td>
<td>APC_00415</td>
<td>numbering 5' of ATG</td>
<td>-</td>
<td></td>
<td></td>
</tr>
<tr>
<td>-?</td>
<td>00</td>
<td>-</td>
<td>c.7T&gt;C</td>
<td>-</td>
<td>-</td>
<td>deletion</td>
<td>APC_00416</td>
<td>numbering 5' of ATG</td>
<td>-</td>
<td></td>
<td></td>
</tr>
<tr>
<td>-?</td>
<td>00</td>
<td>-</td>
<td>c.7insG</td>
<td>-</td>
<td>-</td>
<td>deletion</td>
<td>APC_00417</td>
<td>numbering 5' of ATG</td>
<td>-</td>
<td></td>
<td></td>
</tr>
<tr>
<td>-?</td>
<td>00</td>
<td>-</td>
<td>c.7T&gt;G</td>
<td>-</td>
<td>-</td>
<td>deletion</td>
<td>APC_00418</td>
<td>numbering 5' of ATG</td>
<td>-</td>
<td></td>
<td></td>
</tr>
<tr>
<td>+?</td>
<td>01_15+promoter</td>
<td>del</td>
<td>cytogeneticdeletion</td>
<td>-</td>
<td>-</td>
<td>deletion</td>
<td>APC_00200</td>
<td>cytogenetic deletion</td>
<td>unknown</td>
<td>Raedle et al. 2001</td>
<td></td>
</tr>
<tr>
<td>+?</td>
<td>01_15+promoter</td>
<td>del</td>
<td>cytogeneticdeletion</td>
<td>-</td>
<td>-</td>
<td>deletion</td>
<td>APC_00200</td>
<td>cytogenetic deletion</td>
<td>de novo</td>
<td>Aretz et al. 2005</td>
<td></td>
</tr>
<tr>
<td>+?</td>
<td>01_15+promoter</td>
<td>del</td>
<td>cytogeneticdeletion</td>
<td>-</td>
<td>-</td>
<td>deletion</td>
<td>APC_00200</td>
<td>cytogenetic deletion</td>
<td>de novo</td>
<td>Aretz et al. 2005</td>
<td></td>
</tr>
<tr>
<td>+?</td>
<td>01_15+promoter</td>
<td>del</td>
<td>cytogeneticdeletion</td>
<td>-</td>
<td>-</td>
<td>deletion</td>
<td>APC_00200</td>
<td>cytogenetic deletion</td>
<td>unknown</td>
<td>Aretz and Friedl (unpublished)</td>
<td></td>
</tr>
<tr>
<td>+?</td>
<td>01</td>
<td>24</td>
<td>c.70C&gt;T</td>
<td>-</td>
<td>p.Arg24X</td>
<td>substitution</td>
<td>APC_00551</td>
<td>-</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>+?</td>
<td>01_15</td>
<td>del</td>
<td>g.26940-7_133343+del</td>
<td>-</td>
<td>-</td>
<td>deletion</td>
<td>APC_00587</td>
<td>-</td>
<td>familial</td>
<td></td>
<td>Kantar-Smojer et al. 2008</td>
</tr>
<tr>
<td>+?</td>
<td>01+promoter</td>
<td>del</td>
<td>g.35041-7_52505+del</td>
<td>-</td>
<td>-</td>
<td>deletion</td>
<td>APC_00526</td>
<td>-</td>
<td>familial</td>
<td></td>
<td>Aretz et al. 2005</td>
</tr>
<tr>
<td>+?</td>
<td>01+promoter</td>
<td>del</td>
<td>g.35041-7_52505+del</td>
<td>-</td>
<td>-</td>
<td>deletion</td>
<td>APC_00526</td>
<td>-</td>
<td>familial</td>
<td></td>
<td>Aretz et al. 2005</td>
</tr>
<tr>
<td>+?</td>
<td>01+promoter</td>
<td>del</td>
<td>g.35041-7_52505+del</td>
<td>-</td>
<td>-</td>
<td>deletion</td>
<td>APC_00526</td>
<td>-</td>
<td>familial</td>
<td></td>
<td>Aretz et al. 2005</td>
</tr>
<tr>
<td>+?</td>
<td>01_05+promoter</td>
<td>del</td>
<td>g.35041-7_78383+del</td>
<td>-</td>
<td>-</td>
<td>deletion</td>
<td>APC_00527</td>
<td>-</td>
<td>familial</td>
<td></td>
<td>Aretz et al. 2005</td>
</tr>
</tbody>
</table>
CS Cancer Filtering

MPG>10
  yes
  → MPG/coverage<0.5
  no
  → ClinSeq >1%
  yes
  → stop
  no
  → dbSNP MAF > 0.015 (at least 120 chromosomes)
  yes
  → stop
  no
  → Candidate

HGMD and/or LSDB pathogenicity data

-
  → stop

?
  → VUS
  reevaluate quarterly

+
  → confirm pathogenicity and report
International Association for Research on Cancer (IARC) Pathogenicity Scale

Proposed Classification System for Sequence Variants Identified by Genetic Testing

<table>
<thead>
<tr>
<th>Class</th>
<th>Description</th>
<th>Probability of being pathogenic</th>
</tr>
</thead>
<tbody>
<tr>
<td>5</td>
<td>Definitely pathogenic</td>
<td>&gt;0.99</td>
</tr>
<tr>
<td>4</td>
<td>Likely pathogenic</td>
<td>0.95-0.99</td>
</tr>
<tr>
<td>3</td>
<td>Uncertain</td>
<td>0.05-0.949</td>
</tr>
<tr>
<td>2</td>
<td>Likely not pathogenic or of little clinical significance</td>
<td>0.001-0.049</td>
</tr>
<tr>
<td>1</td>
<td>Not pathogenic or of no clinical significance</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>0</td>
<td>Insufficient information i.e., did not pass quality filter</td>
<td></td>
</tr>
</tbody>
</table>
Summary of Variant Scores
Lessons Learned

• Most variants don’t need neurons
  – Filter away variants that are highly likely benign
  – Set thresholds that reflect best judgment of:
    • Disease biology, medical reality, genetics, & patient attributes

• Focus on those few that do
  – Acquire and display most useful and robust data that can be mustered and think

• Capture and store judgments

• Continually reassess interpretations
What is at Stake

• Among 572 participants *preliminary analysis showed likely pathologic variants for:*
  – 9 with familial hypercholesterolemia
  – 7 with high penetrance Br/Ov Cancer
  – 6 with malignant hyperthermia
  – 3 with HNPP
  – 2 with cardiac dysrythmia