Data sharing in Canada through the COGR: a unified clinical genome database as a community resource for standardizing and sharing genetic interpretations

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Overview

• Grant funded by Genome Canada

• Collaborative effort for the collection, sharing and analysis of variants reported by medical diagnostic laboratories across Canada

• Collaborate with other global initiatives including ClinVar, BRCA Challenge, Human Variome Project
Objectives

• To create Canada’s unified, open-access, clinical-grade genetic database using a commonly shared platform

• Standardize variant assessment procedures

• Data extraction and variant classification consensus building

• Data Access and Disseminate results to a large public repository
Workflow Overview

**Data Collection and Preprocessing**
- Contact sites individually to obtain exports
- Site Storage LIMS / EMS
- Raw Site Export
- Custom Preprocessing Script
- GenelInsight formatted site import

**Data Import and Sharing**
- Upload data onto GenelInsight Instance
- COGR Site-B GenelInsight
- COGR Site-A GenelInsight
- COGR Data Sharing
- COGR Access Policies
  - Based on "Share and Share Alike" or Permission Specific Collaborator Preferences

**COGR Consensus Database & Analysis**
- Variant Discrepancy Assessment
- COGR Consensus Database
- Public Access Database
- COGR Consensus database created by agreement, discussion and curation from lab directors
COGR storage and sharing

• The COGR Consensus Database holds variants with consensus classifications across labs
• Sharing is optional at the discretion of the lab and only enabled upon request
## 23 GeneInsight Instances Created

<table>
<thead>
<tr>
<th>Organization</th>
<th>Upload Status</th>
<th>Sharing Status</th>
</tr>
</thead>
<tbody>
<tr>
<td>Alberta Children's Hospital, Calgary AB</td>
<td>Uploaded</td>
<td>Sharing</td>
</tr>
<tr>
<td>Atlantic Cancer Research Institute, Moncton NB</td>
<td>Pending</td>
<td>-</td>
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<td>British Columbia Cancer Agency, Vancouver BC</td>
<td>Uploaded</td>
<td>Sharing</td>
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<tr>
<td>Children’s &amp; Women’s Health Centre of BC, Vancouver BC</td>
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<tr>
<td>Children's Hospital of Eastern Ontario, Ottawa ON</td>
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<td>Credit Valley Hospital, Trillium Health Centre, Mississauga ON</td>
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<td>Hamilton Health Sciences, McMaster University, Hamilton ON</td>
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<tr>
<td>Impact Genetics Inc., Bowmanville ON</td>
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<td>Memorial Health University Medical Center, St. John’s NL</td>
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<td>North York General Hospital, Toronto ON</td>
<td>Uploaded</td>
<td>Sharing</td>
</tr>
<tr>
<td>Ontario Institute of Cancer Research (OICR), Toronto ON</td>
<td>Uploaded</td>
<td>Sharing</td>
</tr>
<tr>
<td>Regional Health Authority, University of Manitoba, Winnipeg MB</td>
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<tr>
<td>Sainte-Justine Hospital, University of Montreal, Montréal QC</td>
<td>Uploading</td>
<td>-</td>
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<tr>
<td>SickKids Hospital and McLaughlin Centre, Toronto ON</td>
<td>Uploaded</td>
<td>Sharing</td>
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<tr>
<td>Women's College Hospital, University of Toronto, Toronto ON</td>
<td>Uploaded</td>
<td>Sharing*</td>
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</table>

*Also sharing with VariantWire*
COGR Variant Numbers

COGR Comparison 2014/2015

- >17,000 variants
- 1,266 genes
- 66 diseases

<table>
<thead>
<tr>
<th></th>
<th>Variants 2014</th>
<th>Copy Number Variants 2014</th>
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<tbody>
<tr>
<td>2014</td>
<td>3802</td>
<td>3339</td>
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<tr>
<td>2015</td>
<td>12607</td>
<td>4659</td>
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The COGR Recent Initiative

• 2016 marks the COGR’s 4\textsuperscript{th} year
  – Focus to make data holdings both extremely accurate and readily accessible

• Focus on creating and dispersing lab specific discrepancy reports
  – Build consensus clinical interpretations on variants identified in Canadian diagnostic laboratories and academic medical centers
  – Initial project looked at \textit{BRCA1/2}
A. Alberta Children’s Hospital (Calgary, AB)
B. Atlantic Cancer Research Institute (Moncton, NB)
C. British Columbia Cancer Agency (Vancouver BC)
D. Children’s & Women’s Health Centre of BC (Vancouver BC)
E. Children’s Hospital of Eastern Ontario (Ottawa ON)
F. Credit Valley Hospital, Trillium Health Centre (Mississauga ON)
G. Dept of Medical Genetics, University of Alberta (Edmonton, AB)
H. Hamilton Health Sciences, McMaster University (Hamilton, ON)
I. Impact Genetics Inc. (Bowmanville, ON)
J. Izaak Walton Killam Health Centre (Halifax, NS)
K. Kingston General Hospital, Queen’s University (Kingston, ON)
L. McGill University Health Complex (Montréal, QC)
M. Memorial Health University Medical Center (St. John’s, NL)
N. Mount Sinai Hospital, University of Toronto (Toronto, ON)
O. North York General Hospital (Toronto ON)
P. Ontario Institute of Cancer Research (OICR) (Toronto, ON)
Q. Regional Health Authority, University of Manitoba (Winnipeg, MB)
R. Sainte-Justine Hospital, University of Montreal (Montréal, QC)
S. SickKids Hospital and McLaughlin Centre (Toronto, ON)
T. University Hospital, Western University (London, ON)
U. Women’s College Hospital, University of Toronto (Toronto, ON)
V. Jewish General Hospital, Montreal (Montréal, QC)
Discrepancy Report Results Overview

1. Overall discrepancy report results
2. Total changes in classifications and reasoning
3. Changes in discrepant variant classifications
4. Methods for reassessment

- **11** participating labs across 4 provinces
  - ON, BC, AB, MB
- Received total of **5,554** BRCA1/2 variants
  - 3014 unique variants
    - 1,148 seen in >2 labs
    - 110 to 1072 variants per lab (505 on average)
Submission Data - Before Issuing Discrepancy Reports

After data submission 1,148 unique variants were identified in more than one lab

- 550 (48%) of variants had concordant classifications
- 350 (30%) were discordant
- 248 (22%) were unclassified by all labs

*According to 5-tier classification system*
Tiered Discrepancy Systems

- 5-tiered
  - Initially implemented

- 3-tiered
  - Recommended by participants

- 2-tiered
  - Clinical management
After Review of Discrepancy Report Results

- 42% of discordant variants changed classifications
- 28% did not change classifications
- 30% were not reassessed

<table>
<thead>
<tr>
<th>Initial Interpretations</th>
<th># Variants</th>
<th>%</th>
<th>Final Interpretations</th>
<th># Variants</th>
<th>%</th>
<th>Overall Change</th>
</tr>
</thead>
<tbody>
<tr>
<td>Benign</td>
<td>526</td>
<td>37%</td>
<td>637</td>
<td>45%</td>
<td></td>
<td>111 (8%)</td>
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<tr>
<td>Likely Benign</td>
<td>271</td>
<td>19%</td>
<td>321</td>
<td>23%</td>
<td></td>
<td>50 (4%)</td>
</tr>
<tr>
<td>VUS</td>
<td>342</td>
<td>24%</td>
<td>211</td>
<td>15%</td>
<td></td>
<td>127 (9%)</td>
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<tr>
<td>Likely Pathogenic</td>
<td>60</td>
<td>4%</td>
<td>64</td>
<td>5%</td>
<td></td>
<td>4 (&gt;1%)</td>
</tr>
<tr>
<td>Pathogenic</td>
<td>136</td>
<td>10%</td>
<td>170</td>
<td>12%</td>
<td></td>
<td>34 (2%)</td>
</tr>
<tr>
<td>Unclassified</td>
<td>75</td>
<td>5%</td>
<td>9</td>
<td>1%</td>
<td></td>
<td>72 (5%)</td>
</tr>
<tr>
<td>Total</td>
<td>1410</td>
<td></td>
<td>1410</td>
<td></td>
<td></td>
<td>398 (28%)</td>
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Final Discrepancy Results

Number of Unique Variants

<table>
<thead>
<tr>
<th>Concordant</th>
<th>Discrepant</th>
</tr>
</thead>
<tbody>
<tr>
<td>622</td>
<td>278</td>
</tr>
<tr>
<td>770</td>
<td>130</td>
</tr>
<tr>
<td>887</td>
<td>13</td>
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- 5-Tier
- 3-Tier
- 2-Tier
After Review of Discrepancy Report Results

• Only 18% of the discrepant variants reached a consensus for 5-tier system
  – But most labs did not review minor discrepancies
  • Benign vs Likely Benign
  • Pathogenic vs Likely Pathogenic

• In total, for 5-tier system:
  – 69% (622/900) of all unique & classified variants were concordant

• In total, for 3-tier system (LB/B, VUS, LP/P)
  – 86% (770/900) of all unique & classified variants were concordant
Reasoning For Reclassification

• 9 out of 11 labs specified reasoning for some variants
• 64% of reassessed variants provided reclassification reasoning:

- Typographical error: 8%
- Based on new evidence provided: 37%
- Revised classification criteria: 42%
- Other (Please specify): 13%
Methods Used for Reassessment

- Most labs did not review variants through the COGR network
- 8 out of 11 labs specified their reassessment methods
- 34% of variants had specified reassessment methods:

- 43%: We used our own methodology or tools to reassess
- 45%: We used the COGR variant assessment tool (VAT)
- 6%: We used the ACMG reclassification tool provided
- 6%: Other
Summary

• Successful exercise with positive feedback within the COGR community

• Limited resources provide challenges for labs to do this without guidance and help

• Continuing initiatives:
  – Release quarterly discrepancy reports
  – Provide consensus variant interpretations through public database
  – Further collaboration with other international data-sharing efforts including ClinVar, the HVP and the GA4GH
This work was funded by the Government of Canada through Genome Canada and the Ontario Genomics Institute (OGI-070)