Data sharing in Canada through the Canadian Open Genetics Repository

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opengenetics.ca

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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
Clinically validated, de-identified, and approved data

Read-only viewing with ability to validate and import

<table>
<thead>
<tr>
<th>Shared Values</th>
<th>#</th>
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<tbody>
<tr>
<td>Interpreted Variants</td>
<td>~20,000</td>
</tr>
<tr>
<td>Genes</td>
<td>1,298</td>
</tr>
<tr>
<td>Diseases</td>
<td>79</td>
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</tbody>
</table>
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

• **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)
Tiered Discrepancy Models

5-tiered
- Initially implemented

3-tiered
- Recommended by participants

2-tiered
- Clinical management
Data Received

5-tier
- 900 variants had 2 or more classifications
- 350 (38.9%) were discordant
  - 1410 observations of these variants

3-tier
- 240 (26.7%) discordant

2-tier
- 45 (5%) discordant
After analysis

330 (23.8%) discordant variant observations changed classification after analysis

5-tier
- Number of discordant variants decreased from 38.9% to 30.7%

3-tier
- Decrease from 26.7% to 12.45%

2-tier
- Decrease of from 5% to 1%
Classification Changes

Initial variant classifications:
- B: 37
- LB: 19
- VUS: 24
- LP: 4
- P: 10
- Unclassified: 5

Variant classifications after review:
- B: 45
- LB: 23
- VUS: 15
- LP: 5
- P: 12
- Unclassified: 12

Percentage of discordant variants:
Direction of Classification Changes

- **Pathogenic** (n=16)
  - 5
  - 2
  - 3
  - 72
  - 50
- **Likely Pathogenic** (n=19)
  - 14
- **Variant of Uncertain Significance** (n=21)
  - 12
- **Likely Benign** (n=106)
  - 4
  - 34
- **Benign** (n=102)
Reason for Reclassification

- Revised classification criteria: 160
- Based on new evidence provided: 144
- Typographical error: 48
- No classification change: 531
- Other (Please specify): 31

- Typographical error: 8%
- Based on new evidence provided: 13%
- Revised classification criteria: 42%
- Other (Please specify): 37%
We used our own methodology or tools to reassess
We used the COGR variant assessment tool (VAT)
We used the ACMG reclassification tool provided
Take Home

• A Canadian inter-institutional quality improvement program

• Importance of periodic review, tracking and maintaining versioned variant information including for variant classification

• mandatory data submission - proficiency testing, laboratory accreditation

• Real-time reporting of variant data - quality assessment program

• We encourage individual institutions to share their data holdings – generate, maintain and preserve knowledge

• Clinicians using genetic data for risk assessment, diagnosis, prognosis or management of patients should be aware of the variability in variant interpretations