The Canadian Open Genetics Repository (COGR): a Cross-Laboratory Case Study in Sharing *BRCA1* and *BRCA2* Clinical Variant Interpretations

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Background

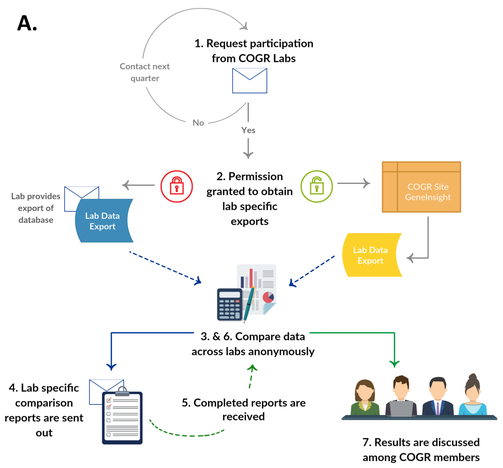
The COGR present findings from a multi-laboratory study in sharing clinical DNA variant interpretations from *BRCA1* and *BRCA2* genes.

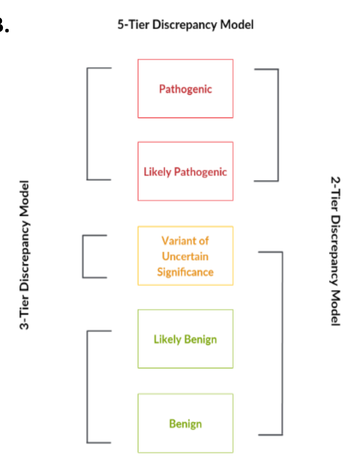
The COGR is a collaborative effort for the collection, storage, sharing and analysis of variants reported by 22 medical diagnostics laboratories across Canada. The inherent collaborative structure of the COGR promotes real-time sharing between geographically distant laboratories and enhances the exchange of information about DNA variants within the expert community utilizing Geneinsight software.

The COGR currently has 50% of participating laboratories actively sharing data. The platform has over 18,000 variants uploaded encompassing 1,298 genes and 79 diseases.

The objective of this study was to develop a national program to foster comparison and reassessment of DNA variant interpretations between laboratories and resolve identified discordances, using *BRCA1* and *BRCA2* genes as a case study.

Consensus Building Workflow





A. The workflow used to build consensus on variant interpretations identified in participating labs: (1-2) Labs were requested to submit their data. (3) After collection of all variant data holdings, variant interpretations were compared across labs. (4) To allow labs the opportunity to reclassify variants lab specific comparison reports were issued. (6) Completed comparison reports were collected, reanalyzed and (7) results were discussed among participants.

B. The three independent tier models used to determine variant concordance across laboratories.

Comparison Reports

Issued comparison reports were structured into three main sections:

i. **Concordant variants** - variants seen in at least two laboratories with variant interpretations in agreement

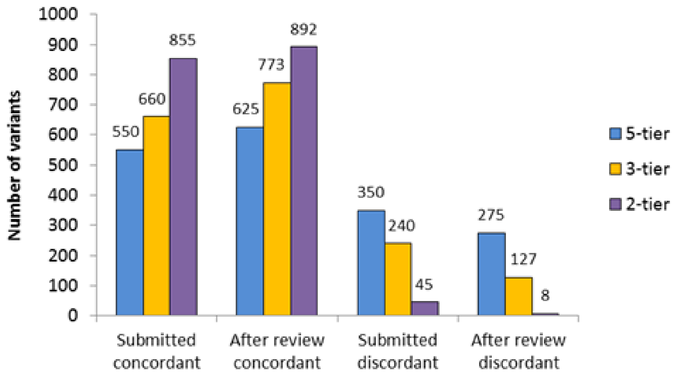
ii. **Variant unique to a lab** – variants only seen in one laboratory

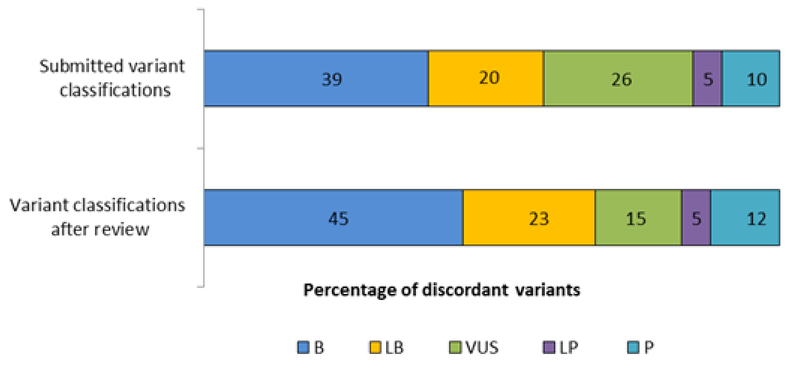
iii. **Discordant variants** – variants seen in at least two laboratories with variant interpretations in disagreement

For each variant, laboratories were provided variant details and their current variant interpretation. For discrepant variants laboratories were also provided with anonymized data showing how their variant classification compared to other laboratories.

Evidence was provided for each variant if available and laboratories used either a variant assessment tool provided by the COGR or proprietary methods combined with ACMG 2015 guidelines for interpreting variants.

Results & Discussion





There were a total of 5,554 (3,014 unique) *BRCA1* and *BRCA2* variant observations submitted from 11 participating laboratories across four provinces (ON, BC, AB, MB). Of the unique variants, 900 were classified in two or more laboratories. Based on the 5-tiered model 550 (61%) of variants had concordant classifications and 350 (39%) were discordant. After review of the comparison reports, 75 variants reached concordance and 275 remained discordant.

After comparing discordances, 42% of variants changed classifications, 23% did not change and 32% were not reassessed. Reasoning for reclassification was specified for 85.3% of the reclassified variants and was primarily due to either revised interpretation criteria or based on new evidence provided. After reclassification, the percentage of benign (B) and likely benign (LB) variants increased whereas variants of uncertain significance (VUS) and pathogenic (P) decreased. No reclassified variants changed from LB/B to LP/P or vice versa, highlighting the thorough nature of the submitted classifications.

Conclusion

Here we describe a Canadian inter-institutional quality improvement program for DNA variant interpretations. All participating labs were not previously aware of their variant interpretation discordances nor was there a mechanism in place to allow the analysis of variant data across Canadian institutions prior to the creation of the COGR. We aimed to arrive at a consensus for variant interpretations and reduce variant classification differences between professionals reporting on *BRCA1* and *BRCA2* variant data.

The COGR encourages the collaboration of Canadian institutions to share their data holdings in pursuance of the generation, maintenance and reservation of knowledge. Furthermore, the COGR aims to continue fostering further collaboration with other international data-sharing efforts including VariantWire, ClinVar, and the Global Alliance for Genomics and Health.

The sharing of variant knowledge by clinical diagnostic laboratories will allow clinicians and patients to make more informed decisions and will ultimately lead to better patient outcomes.

Want to learn more? Contact us! Email: cogr@opengenetics.ca Web: http://opengenetics.ca

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