ClinGen and ClinVar: Complementary Resources

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ClinGen and ClinVar: What’s the Difference?

• ClinGen and ClinVar work together to provide complementary resources to support genomic interpretation

• ClinVar is a DATABASE funded by intramural NIH funding and maintained by the NCBI
  • Goal: Public archive of [any] reports of the relationships between [any] variants and [any] conditions

• ClinGen is a PROGRAM funded by NHGRI
  • Goal: Identifying *clinically relevant* genes and variants for use in precision medicine and research
What is ClinVar?

- Public archive of variant-phenotype assertions, submitted from a variety of sources, including:
  - Clinical laboratories
  - Research projects
  - Expert panels
  - Other databases, etc.

- Different from dbSNP, dbVar, which primarily maintain information about locations, types of variants
What does ClinVar DO?

• Facilitates the evaluation of variant-phenotype assertions by:
  • Archiving submitted interpretations of gene-disease relationships
  • Aggregating data from multiple submitters
  • Determine if there is a consensus about the interpretation

• ClinVar DOES NOT interpret variants!
What’s currently in ClinVar?

<table>
<thead>
<tr>
<th>Category of analysis</th>
<th>Current total (Aug 13, 2018)</th>
</tr>
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<tbody>
<tr>
<td>Records submitted</td>
<td>700611</td>
</tr>
<tr>
<td>Records with assertion criteria</td>
<td>566125</td>
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<tr>
<td>Records with an interpretation</td>
<td>683254</td>
</tr>
<tr>
<td>Total genes represented</td>
<td>30190</td>
</tr>
<tr>
<td>Unique variation records</td>
<td>441973</td>
</tr>
<tr>
<td>Unique variation records with interpretations</td>
<td>431693</td>
</tr>
<tr>
<td>Unique variation records with assertion criteria</td>
<td>369351</td>
</tr>
<tr>
<td>Unique variation records with practice guidelines (4 stars)</td>
<td>23</td>
</tr>
<tr>
<td>Unique variation records from expert panels (3 stars)</td>
<td>10423</td>
</tr>
<tr>
<td>Unique variation records with assertion criteria, multiple submitters, and no conflicts (2 stars)</td>
<td>60340</td>
</tr>
<tr>
<td>Unique variation records with assertion criteria (1 star)</td>
<td>280110</td>
</tr>
<tr>
<td>Unique variation records with assertion criteria and a conflict (1 star)</td>
<td>18455</td>
</tr>
<tr>
<td>Unique variation records with conflicting interpretations</td>
<td>18608</td>
</tr>
<tr>
<td>Genes with variants specific to one gene</td>
<td>6053</td>
</tr>
<tr>
<td>Genes with variants specific to one protein-coding gene</td>
<td>5942</td>
</tr>
<tr>
<td>Genes included in a variant spanning more than one gene</td>
<td>30153</td>
</tr>
<tr>
<td>Variants affecting overlapping genes</td>
<td>13913</td>
</tr>
<tr>
<td>Total submitters</td>
<td>1021</td>
</tr>
</tbody>
</table>
ClinVar is a submitter-driven resource

• There are many pieces of information that ClinVar CAN collect on a variant, but *if a submitter does not submit them, they aren’t available.*

• Quality of submissions vary

• When assessing the information you find in ClinVar, you must assess the quality of the submitter/submission itself
Assessing Quality in ClinVar

• IN GENERAL, one mark of a submission’s quality is it’s review level – at minimum, you should be able to figure out the methods by which the variant was evaluated

• These are known as “assertion criteria”

• When a submitter provides assertion criteria, the submission receives at least 1 star
Clinical Laboratories Meeting Minimum Requirements for Data Sharing to Support Quality Assurance

ClinGen considers the sharing of variant interpretations essential for supporting genomic medicine and a critical part of quality assurance for accurate genetic and genomic testing. Open and transparent sharing allows peer-review and knowledge dissemination to ensure the highest quality care of patients.

Here, we identify clinical laboratories who meet a minimum standard of data sharing:

- Laborotary submissions are registered in ClinVar as 'Single Submitter, Assertion criteria provided' (single star)
- Laboratory registered in the Genetic Test Registry (GTR) with up-to-date yearly review
- Laboratory submits at least once per year adding new variants and updating reclassified variants as necessary
- Laboratory submits all categories of variants returned to patients (labs are also encouraged to share B/L/E/VUS variants even if not returned)
- Laboratory has attested to submitting at least 75% of all sequence and/or copy number variants reported in the past year
- Laboratory has submitted at least 100 variants
- Laboratory is CLIA certified laboratory (USA) or meets an equivalent standard in another country

To apply for status, or to update your status, laboratories can apply here.

Questions about the criteria? Visit our Frequently Asked Questions or contact clingen@clinicalgenome.org.
<table>
<thead>
<tr>
<th>Laboratory</th>
<th>Meets requirements</th>
<th>Additional Achievements</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>Submitted evidence</td>
</tr>
<tr>
<td>Ambry</td>
<td>✔</td>
<td>✔</td>
</tr>
<tr>
<td>ARUP</td>
<td>✔</td>
<td>✔</td>
</tr>
<tr>
<td>Athena Diagnostics Inc.</td>
<td>✔</td>
<td>✔</td>
</tr>
<tr>
<td>Centre for Mendelian Genomics, University Medical Centre Ljubljana</td>
<td>✔</td>
<td>✔</td>
</tr>
<tr>
<td>Center for Pediatric Genomic Medicine, Children’s Mercy Hospital and Clinics</td>
<td>✔</td>
<td>✔</td>
</tr>
<tr>
<td>Color Genomics, Inc.</td>
<td>✔</td>
<td>✔</td>
</tr>
<tr>
<td>Coensyl</td>
<td>✔</td>
<td>✔</td>
</tr>
<tr>
<td>EGL Genetics (Emory)</td>
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<td>✔</td>
</tr>
<tr>
<td>GeneDx</td>
<td>✔</td>
<td>✔</td>
</tr>
<tr>
<td>GeneKor MSA</td>
<td>✔</td>
<td>✔</td>
</tr>
<tr>
<td>Illumina</td>
<td>✔</td>
<td>✔</td>
</tr>
<tr>
<td>Integrated Genetics/Laboratory Corporation of America</td>
<td>✔</td>
<td>✔</td>
</tr>
<tr>
<td>Invitae</td>
<td>✔</td>
<td>✔</td>
</tr>
<tr>
<td>Partners Laboratory for Molecular Medicine</td>
<td>✔</td>
<td>✔</td>
</tr>
<tr>
<td>Phosphorus Diagnostics LLC</td>
<td>✔</td>
<td>✔</td>
</tr>
<tr>
<td>Quest Diagnostics Nichols Institute San Juan Capistrano</td>
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<td>✔</td>
</tr>
<tr>
<td>University of Chicago</td>
<td>✔</td>
<td>✔</td>
</tr>
</tbody>
</table>
What is the Clinical Genome Resource (ClinGen)?

ClinGen's Critical Questions

- Is this gene associated with a disease? (Clinical Validity)
- Is this variant causative? (Pathogenicity)
- Is this information actionable? (Clinical Utility)

Building a Genomic Knowledge Base

ClinVar & Other Resources

Improved Patient Care Through Genomic Medicine
ClinGen’s Curation Efforts
Which variants in a gene actually cause disease?

• Several different efforts going on in this space
  • Addressing existing classification disagreements: Inter-laboratory discrepancy resolution
    • Sequence and copy number variants
  • Preventing future classification disagreements: Modifications of the current ACMG/AMP sequence variant guidelines (Sequence Variant Interpretation WG)
    • General/quantitative specifications of current guidelines
    • Disease-specific modifications

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Discrepancy Resolution Efforts

Resolved 87.2% of discordant sequence variant classifications between participating labs

Updated classifications for 63.8% of CNVs evaluated overlapping dosage sensitive genes
ACMG/AMP Guidelines

ClinGen Expert Panels

- Cardiovascular
- Neurodevelopmental Disorders
- Hereditary Cancer
- Metabolism
- RASopathies, etc.

Sequence Variant Interpretation WG
Harmonize recommendations for modifying ACMG guidelines

Gene/Disease Specific ACMG Guidelines

General recommendations to ACMG Guidelines

Slide courtesy of Steven Harrison, PhD
ClinGen’s Curation Efforts

- Gene-Disease Validity
  - Can variation in this gene cause disease?
  - Learn more »

- Variant Pathogenicity
  - Which changes in this gene cause disease?
  - Learn more »

- Clinical Actionability
  - How does this genetic diagnosis impact medical management?
  - Learn more »

- Dosage Sensitivity
  - Is haploinsufficiency or triposensitivity an established disease mechanism for this gene?
  - Learn more »
Does this gene, when significantly altered, cause this disease?
• Defines the criteria needed to assess (genetic evidence, gene-level experimental evidence)
• Describes the strength evidence supporting a gene-disease relationship in a semi-quantitative manner
• Allows users to methodically classify the validity of a given gene-disease pair

The American Journal of Human Genetics 100, 895-906, June 1, 2017 895

Evaluating the Clinical Validity of Gene-Disease Associations: An Evidence-Based Framework Developed by the Clinical Genome Resource

Natasha T. Strande,1,14 Erin Rooney Riggs,2,14 Adam H. Buchanan,3 Ozge Ceyhan-Birsoy,4,5,6,7 Marina DiStefano,4 Selina S. Dwight,8 Jenny Goldstein,1 Rajarshi Ghosh,9 Bryce A. Seifert,1 Tam P. Sneddon,5 Matt W. Wright,8 Laura V. Milko,1 J. Michael Cherry,8 Monica A. Giovanni,3 Michael F. Murray,3 Julianne M. O’Daniel,1 Erin M. Ramos,10 Avni B. Santani,11,12 Alan F. Scott,13 Sharon E. Plon,9 Heidi L. Rehm,4,5,6,7 Christa L. Martin,4,5,6,7 and Jonathan S. Berg1,*
<table>
<thead>
<tr>
<th>Definitive</th>
<th>Role has been repeatedly demonstrated in research &amp; clinical diagnostic settings • Upheld over time (in general, at least 3 years) • No convincing contradictory evidence</th>
</tr>
</thead>
<tbody>
<tr>
<td>Strong</td>
<td>≥2 independent studies with: • Multiple pathogenic variants in unrelated probands • AND • Several different types of supporting experimental data • OR • Excess of pathogenic variants in cases vs. controls • No convincing contradictory evidence</td>
</tr>
<tr>
<td>Moderate</td>
<td>Several unrelated probands with pathogenic variants • Some supporting experimental data • No convincing contradictory evidence</td>
</tr>
<tr>
<td>Limited</td>
<td>&lt;3 unrelated probands with pathogenic variants • OR • Multiple variants reported in unrelated probands but without sufficient evidence for pathogenicity • No convincing contradictory evidence</td>
</tr>
<tr>
<td>No Evidence Reported</td>
<td>No evidence reported for a causal role in disease (candidate genes, etc.), therefore no pathogenic variants have been identified in humans to date.</td>
</tr>
<tr>
<td>Conflicting Evidence Reported</td>
<td>Disputed</td>
</tr>
<tr>
<td>Conflicting Evidence Reported</td>
<td>Refuted</td>
</tr>
</tbody>
</table>
Using Gene-Disease Validity in Clinical Practice

• Laboratory: test design

• Clinician: Test ordering – which panel to choose?
  • May consider ordering only panels with established genes
  • Bigger is not always better!

• Clinician: Result interpretation – dealing with results in genes of uncertain significance
ClinGen’s Curation Efforts

- Gene-Disease Validity
  - Can variation in this gene cause disease?
  - Learn more »

- Variant Pathogenicity
  - Which changes in this gene cause disease?
  - Learn more »

- Clinical Actionability
  - How does this genetic diagnosis impact medical management?
  - Learn more »

- Dosage Sensitivity
  - Is haploinsufficiency or triposensitivity an established disease mechanism for this gene?
  - Learn more »
Is a gene or genomic region dosage sensitive?

- Originally created in 2011 as a resource to assist in the interpretation of copy number variants (ISCA, ICCG, ClinGen)
- Evidence-based process to assess genes and regions for dosage sensitivity
  - Haploinsufficiency
  - Triplosensitivity
- Goal: to create a genome-wide dosage sensitivity map

Towards an evidence-based process for the clinical interpretation of copy number variation


The evidence-based review (EBR) process has been widely used to develop standards for medical decision-making and to explore complex
### Efficient Evidence
- At least 3 independent losses of function mutations or duplications in unrelated individuals with a similar phenotype and CINE of the following:
  - Mutations are found in at least 2 separate publications. OR
  - Mutations are found in a single publication, but supporting secondary evidence is present
- Role of mutations in normal populations must be understood
  - Mutations are not observed in normal populations. OR
  - Associations between phenotype and incomplete penetrance and/or variable expressivity are well documented

**Potential Clinical Interpretation:** Pathogenic

### Emerging Evidence
- Two independent losses of function mutations or duplications in unrelated individuals with a similar phenotype
  - OR
- More than 2 mutations as described above, but the mutations are either:
  - Inherited from normal parents, and the spectrum of incomplete penetrance/variable expressivity is not understood. OR
  - Not significantly enriched in clinical populations when compared to controls
  - Observed amongst clinical populations at a statistically significant level in more than one large-scale case control series, without a well-described phenotypic association

**Potential Clinical Interpretation:** Uncertain, Likely Pathogenic OR Uncertain

### Little Evidence
- A single loss of function mutation or duplication in an individual with a clinical phenotype
  - OR
- Observed amongst clinical populations at a statistically significant level in a single large-scale case-control series, without a well-described phenotypic association
  - OR
- Only secondary evidence available to support possible dosage sensitivity

**Potential Clinical Interpretation:** Uncertain

### No Evidence
- No loss of function mutations or duplications reported in probands with a clinical phenotype

**Potential Clinical Interpretation:** Uncertain OR Uncertain, Likely Benign

### Dosage Sensitivity is Unlikely
- Only evidence refuting the region's dosage sensitivity (e.g., significant observation in normal population, etc.) has been reported

**Potential Clinical Interpretation:** Uncertain, Likely Benign OR Benign
Using Dosage Sensitivity in Clinical Practice

• Interpreting copy number variants
  • Which genes in the deleted/duplicated region are dosage sensitive?

• Beyond copy number variants...
  • Which diseases are potentially caused by LOF mechanism?
ClinGen’s Curation Efforts
Which genes, when significantly altered, confer a high risk of serious disease that could be prevented or mitigated if the risk were known?
<table>
<thead>
<tr>
<th>Domain</th>
<th>Scores</th>
</tr>
</thead>
</table>
| **Severity:** what is the nature of the threat to health to an individual carrying a clearly deleterious allele in this gene? | 3 = Reasonable possibility of sudden death  
2 = Reasonable possibility of death or major morbidity  
1 = Modest morbidity  
0 = Minimal or no morbidity |
| **Likelihood of disease:** what is the chance that a serious outcome will materialize given a deleterious variant (akin to penetrance)? | 3 = >40% chance  
2 = 5–39% chance  
1 = 1–4% chance  
0 = <1% chance |
| **Effectiveness of specific interventions:** how effective is the selected, specific intervention for preventing or significantly diminishing the risk of harm? | 3 = Highly effective  
2 = Moderately effective  
1 = Minimally effective  
\text{IN} = \text{Ineffective/no intervention} |
| **Nature of intervention:** how risky, medically burdensome, or intensive is a given intervention? | 3 = Low risk, or medically acceptable and low-intensity interventions  
2 = Moderate risk, moderately acceptable or intensive interventions  
1 = Greater risk, less acceptable and substantial interventions  
0 = High risk, poorly acceptable or intensive interventions |
| **State of the knowledge base:** what is the level of evidence? | A = Substantial evidence, or evidence from a high tier (tier 1)  
B = Moderate evidence, or evidence from a moderate tier (tier 2)  
C = Minimal evidence, or evidence from a lower tier (tier 3 or 4)  
D = Poor evidence, or evidence not provided in the report  
E = Evidence based on expert contributions (tier 5) |

\*Do not score the remaining categories.
Using Clinical Actionability in Clinical Practice

• May help guide return of secondary or incidental findings
• Actionability reports provide a comprehensive overview of clinical features, natural history, and management recommendations based on published guidelines
Acknowledgements

• ClinGen PIs and working group members
  • >570 individuals from >230 institutions worldwide
  • Funding: NIH/NHGRI U41HG006834, U41HG009649, U41HG009650

• ClinVar staff
  • Team lead: Melissa Landrum

• Questions?
  • eriggs@geisinger.edu
  • clingen@clinicalgenome.org