ClinGen
Clinical Genome Resource

Module: Variant Interpretation Discrepancy Resolution

Category: Performance and Practice - Part IV

Introduction

More than 80 million genomic variants have been identified in the human genome, yet the effect of most on health and disease is unknown. In the last few years, many laboratories committed to improving knowledge of genomic variation have begun sharing their variant classifications in ClinVar (https://www.ncbi.nlm.nih.gov/clinvar/). The ClinVar database is maintained by the National Center for Biotechnology Information (NCBI) and provides a freely available archive of reports of relationships among human variants and phenotypes. Variants and supporting evidence can be submitted by researchers, clinical laboratories, expert groups, clinicians, and patients registries. Sharing of genomic variants and their classifications is supported and facilitated by the National Institutes of Health (NIH)-funded Clinical Genome Resource (ClinGen) https://www.clinicalgenome.org/.

Currently, a number of variants in ClinVar have been submitted by multiple submitters. In a number of instances, interpretations from different sources, including operating clinical laboratories, have different clinical significance assertions for the same variant.[1,2] Updated standards for interpreting genomic variants have provided structured guidelines for evaluating sequence and structural variants and have allowed laboratories to resolve some differences in interpretation.[3] However, discrepancies between testing laboratories remain due to differing interpretation methods, timepoints of interpretation, access to non-public evidence, and subjectivity in evidence evaluation.

ClinVar provides a monthly report of all conflicting interpretations (Go to ftp://ftp.ncbi.nlm.nih.gov/pub/clinvar/tab_delimited/ and click on "Summary of conflicting interpretations.txt") and ClinGen represents this data in a web-accessible interface (http://variantexplorer.org). This data provides a logical mechanism for practice improvement for laboratory directors in which laboratories could collaborate to address these discrepancies. Several studies have shown that such efforts commonly lead to resolution of differences.[4,5,6] Collaboration to potentially resolve discrepant assertions, when possible, could lead to a more accurate reference database and to better health care for patients who harbor these variants.

References

1. Rehm, H. L., Berg, J. S., Brooks, L. D., Bustamante, C. D., Evans, J. P., Landrum, M. J., . . . Watson, M. S. (2015). ClinGen — The Clinical Genome Resource. New England Journal of Medicine, 372(23), 2235-2242. doi:10.1056/nejmsr1406261
2. Pepin, M. G., Murray, M. L., Bailey, S., Leistritz-Kessler, D., Schwarze, U., & Byers, P. H. (2015). The challenge of comprehensive and consistent sequence variant interpretation between clinical laboratories. Genetics in Medicine, 18(1), 20-24. doi:10.1038/gim.2015.31
3. Richards, S., Aziz, N., Bale, S., Bick, D., Das, S., Gastier-Foster, J., . . . Rehm, H. L. (2015). Standards and guidelines for the interpretation of sequence variants: a joint consensus recommendation of the American College of Medical Genetics and Genomics and the Association for Molecular Pathology. Genetics in Medicine, 17(5), 405-423. doi:10.1038/gim.2015.30
4. Garber, K., Vincent, L., Alexander, J., Bean, L., Bale, S., & Hegde, M. (2016). Reassessment of Genomic Sequence Variation to Harmonize Interpretation for Personalized Medicine. The American Journal of Human Genetics, 99(5), 1140-1149. doi:10.1016/j.ajhg.2016.09.015
5. Amendola, L. M., Jarvik, G. P., Leo, M. C., Mclaughlin, H. M., Akkari, Y., Amaral, M. D., . . . Rehm, H. L. (2016). Performance of ACMG-AMP Variant-Interpretation Guidelines among Nine Laboratories in the Clinical Sequencing Exploratory Research Consortium. The American Journal of Human Genetics, 98(6), 1067-1076. doi:10.1016/j.ajhg.2016.03.024
6. Harrison, S. Dolinsky, J.S., Knight Johnson, A.E., Pesaran, T., Azzariti, D.R., Bale, S., . . . Rehm, H.L. (2017). Clinical Laboratories Collaborate to Resolve Differences in Variant Interpretations Submitted to ClinVar. Genetics in Medicine. doi:10.1038/gim.2017.14.

Practice Profile/Assessment

Laboratory geneticists completing this module must be from a laboratory that regularly submits to the ClinVar database. If you have not submitted to ClinVar before or need additional information about how to submit, information can be found here: https://www.ncbi.nlm.nih.gov/clinvar/docs/submit/.

A monthly report is generated by ClinVar listing all differences in interpretation between submitters. The report is released at the beginning of each month on ClinVar's FTP site: Go to ftp://ftp.ncbi.nlm.nih.gov/pub/clinvar/tab_delimited/ and click on "Summary of conflicting interpretations.txt". Of note, the monthly report lists any difference in interpretation between submitters, including differences in confidence or "likelihood" (Difference between Benign and Likely Benign or Pathogenic and Likely Pathogenic). For the purpose of this exercise, discrepancies will be defined as those between the three major classification levels: "pathogenic (P) / likely pathogenic (LP)", "uncertain significance (VUS)", and "likely benign (LB) / benign (B)". These differences are reported by ClinVar as conflicting interpretations, as indicated by the "Conflict_Reported" column in the monthly report.

The information from the monthly report is also available through a web-based tool developed by ClinGen (https://www.clinicalgenome.org/variant-assertion-discrepancy-resolution/).

For variants that have a difference between the three major classification levels: "pathogenic (P) / likely pathogenic (LP)", "uncertain significance (VUS)", and "likely benign (LB) / benign (B)" between the submitting laboratory (laboratory A)

and at least one 'criteria provided, single submitter' laboratory, the individual completing the module should attempt to resolve classification discrepancies. This process may include re-evaluating the variant internally. Alternatively, the individual completing the module may need to work with one or more other submitters to resolve the discrepancy. Priority should be given to medically significant discrepancies (e.g., P/LP vs VUS/LB/B) but VUS vs LB/B differences can be used for this exercise.

The individual working to resolve a discrepancy should reassess the variant, using interpretation criteria consistent with ACMG-AMP guidelines, if not applied previously. If the individual completing the module needs to contact other submitters, contact information may be found in the ClinVar submission by clicking on the submitter. If the submitter page does not include this information, contact information may be found on the web such as on the submitter's website. If multiple submitters work together to resolve a variant discrepancy, the variant reassessment should also include internal data from all submitters, if available.

If variant interpretations are updated after reassessment and discussion, they should be resubmitted to ClinVar according to instructions provided on the ClinVar website: https://www.ncbi.nlm.nih.gov/clinvar/docs/submit/#update.

For each resolved discrepancy, the following information should be tracked for ABMGG documentation of practice improvement:

1. Your laboratory's initial classification
2. Variant ClinVar ID(s)
3. Other laboratories' classifications
4. Reason for initial discrepancy
5. Outcome of the reassessment including the updated classification (if modified)
6. Remaining reason for any remaining discrepancy
7. Date analysis was completed
8. Information about updating ClinVar submission(s) if needed

Any laboratory geneticists participating in this exercise can submit this module for MOC Practice Improvement.

To receive credit, laboratory geneticists must complete this module for three variants. If a participant's own laboratory interpretation has changed on the basis of this exercise, the updated interpretation must be resubmitted to ClinVar (see instructions for updating ClinVar entries under the "Update your submission" section here: https://www.ncbi.nlm.nih.gov/clinvar/docs/submit/#update). Once the module has been completed for three variants, please email the three completed PDF documents to clingen@clinicalgenome.org. ClinGen staff will then review the module for completeness. If the module is completed at a satisfactory level, a certificate will be sent to your email address. The certificate can then be submitted to ABMGG via the ABMGG portal for Part IV credit.

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Your Information

Full Name

Email Address

Phone Number

Laboratory Name

City & State

Country

Step 1 - About Your Variant

1. ClinVar Variant ID

ClinVar ID

The variant ID is located at the top of the ClinVar site for that variant.

2. Is this a sequence or copy number variant?

Sequence Variant

Gene

Variant

Please provide transcript and HGVS (For example NM_002496.3:c.64C>T) or genomic coordinate and browser build (chr11:g.67799758C>T (hg19))

Copy Number Variant

ISCN/CNV

Specify the overlapping variants you are evaluating using ISCN Nomenclature or genomic coordinates. Separate multiple variants with a colon (:). You can identify overlaps by using the NCBI's variant viewer (https://www.ncbi.nlm.nih.gov/variation/view/) or UCSC genome browser (https://genome.ucsc.edu/).

List ClinVar IDs

Specify the ClinVar Variant or dbVar IDs for these variants. Separate multiple IDs with a colon (:).

3. Your Laboratory Variant Classification (Initial)

Pathogenic	Likely Pathogenic	Uncertain Significance
Likely Benign	Benign	Other

4. Please provide information about the 'criteria provided, single submitter laboratory that also classified this variant. Please indicate the number of 'criteria provided, single submitter' laboratory(ies) that classified the variant as one of the following classifications:

Pathogenic	Likely Pathogenic	Uncertain Significance
Likely Benign	Benign	Other

Step 2 - Reassessment

5. Indicate the reason or reasons for the initial classification discrepancy.

Updated variant information that alters interpretation

Other laboratory had an outdated submission in ClinVar

Outdated interpretation criteria used

Differences in use of or weight given to public data

Differences in internal data

Other

6. Did you need to contact any other 'criteria provided, single submitter' laboratories to discuss and reassess this variant?

Yes If yes, how many 'criteria provided, single submitter' laboratories did you work with to attempt to resolve this discrepancy?

1 2 3 4 5 6 7 8 9 10+

No

7. Please list the names of any other 'criteria provided, single submitter' laboratories you worked with to attempt to resolve this discrepancy.

8. What was the outcome of your reassessment?

   Your laboratory reassessed the variant and updated the classification and it is now in accordance with other submitters.

   Other laboratories reassessed the variant and agreed with your laboratory's interpretation, resolving the discrepancy.

   The variant was discussed but laboratories are still in disagreement. Check all that apply:

      Some laboratories, but not all, changed interpretations

      One or more laboratories were non-responsive

      A medically significant discrepancy was reduced to a non-medically significant discrepancy (benign/likely benign versus pathogenic/likely pathogenic has been reduced to benign/likely benign versus uncertain significance)

      Laboratories agree on the evidence but use different terms to classify the variant

      Laboratories disagreed on application of ACMG/AMP criteria

      Laboratories disagreed on source of primary evidence

      Other, please specify

9. Your Laboratory Variant Classification Following the Exercise

Pathogenic	Likely Pathogenic	Uncertain Significance
Likely Benign	Benign	Other

10. If your classification now differs from your initial interpretation, you must update your ClinVar submission. Please note the status of your update. *Please note that credit for the module will be withheld until an updated ClinVar submission is complete.*

    Update submitted and posted in ClinVar

    Update submitted but not yet posted in ClinVar

    Update will be submitted with my laboratory's next submission scheduled for:

    Other

11. If another submitter(s) agreed to change their interpretation, what is the status of the update in ClinVar?

    Update submitted and posted in ClinVar

    Update submitted but not yet posted in ClinVar

    Submitter agreed to update but has not yet submitted

    Other

12. Comments

Step 4 - Digital Signature

Provide your name and digital signature below. Clicking the signature field will prompt you to sign and save the final file. Remember to follow the module submission process as outlined below.

Your Full Name

Adobe Digital Signature

Learn about digital signatures at https://helpx.adobe.com/acrobat/using/digital-ids.html

Step 5 - Module Submission Process

This module will not be reviewed unless you complete the following;

1. To receive credit, laboratory geneticists must complete this module for **three** variants.
2. For each of the variants, the discrepancy must be a difference between the three major classification levels: "pathogenic (P) / likely pathogenic (LP)", "uncertain significance (VUS)", and "likely benign (LB) / benign (B)."
3. Once the module has been completed for **three** variants, you can submit by emailing the three completed PDF documents to clingen@clinicalgenome.org. ClinGen staff will then review the module for completeness. If the module is completed at a satisfactory level, a certificate will be sent to your email address. You can then submit the certificate to ABMGG via the ABMGG portal for Part IV credit. Please note that credit for the module will be withheld until an updated submission to ClinVar is complete (if applicable).