Variant classifications are highly concordant in ClinVar but with variability in genes from different disease areas

Shan Yang, Stephen Lincoln, Keith Nykamp, Tina Hambuch, Yuya Kobayashi, Scott Topper, Robert Nussbaum

Invitae, San Francisco, CA

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Introduction

Clinical genetic tests of germline DNA are routinely used to direct patient care in oncology, cardiology, neurology, pediatrics, obstetrics, and other clinical specialties. As the number of laboratories offering genetic tests grows and testing menus expand, the potential for inconsistent variant classifications increases. Public databases of clinically classified variants afford, for the first time, the ability to evaluate this issue systematically.

ClinVar Data Set, Methods, and Definitions

All evaluated pathogenicity assessments were based on the ClinVar (www.ncbi.nlm.nih.gov/clinvar/) September 2016 XML file [1, 2].

- After parsing the XML file, we filtered, cleaned, and merged all variants if needed. Only variants with at least two valid submissions were analyzed.
- Each variant was assigned to one or two disease areas based on the primary function of its gene.

Definitions

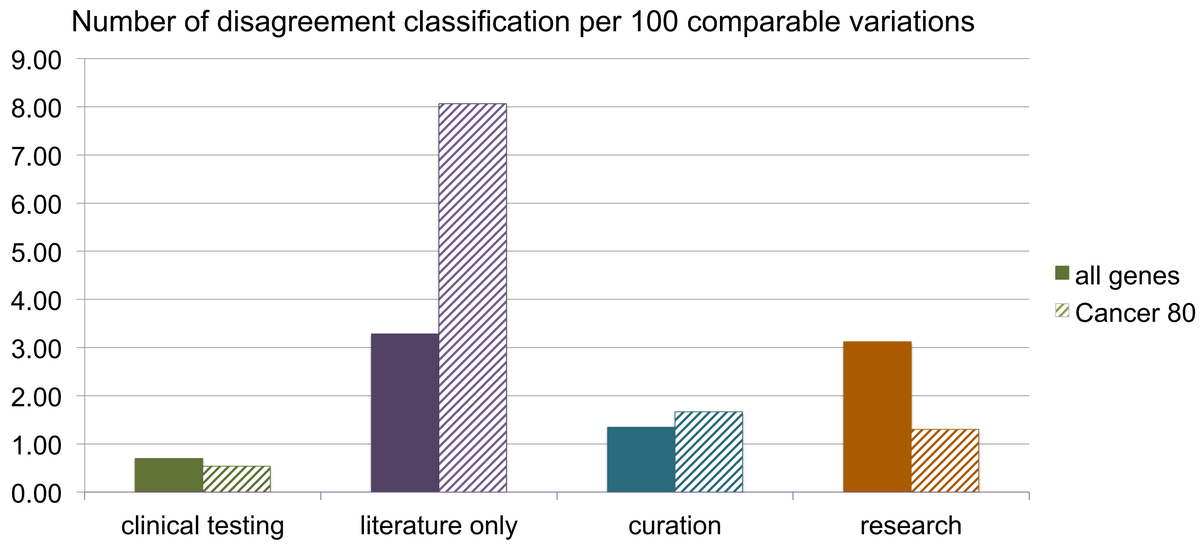
- **Consensus:** More than 65% of submitters agree on the same classification.
- **All agree:** All (100%) submitters agree on the same classification.
- **Disagreement:** a submission that disagrees with the consensus
- **P classification:** Pathogenic (P) and Likely pathogenic (LP)
- **U classification:** Uncertain significance (or VUS)
- **B classification:** Benign (B) and Likely benign (LB)
- **NP (non-P) classification:** Benign, Likely Benign, and Uncertain significance

Results

Overall, classifications in ClinVar submitted through all collection methods were found to be highly concordant. Among 23,944 comparable variants (with ≥ 2 submissions), 96.35% (23,071) had consensus for clinically actionable (P) and non-actionable (NP) classifications, and 93.57% (22,405) had agreement among all submitters for P and NP classifications. Considering that benign variants are not commonly submitted to ClinVar, we believe that concordance is much higher than these percentages indicate.

ClinVar concordance rate by collection method

Interestingly, “literature only” submissions have a very high disagreement rate (most commonly from OMIM [3]) with consensus classification, whereas “clinical testing” submissions have a very low disagreement rate with the consensus. “Curation” and “research” submissions have disagreement rate lower than those of literature only submissions but higher than those of clinical testing submissions. This outcome is intuitive because clinical laboratories generally use rigorous and similar classification criteria (e.g., ACMG 2015 guidelines [4]).



References

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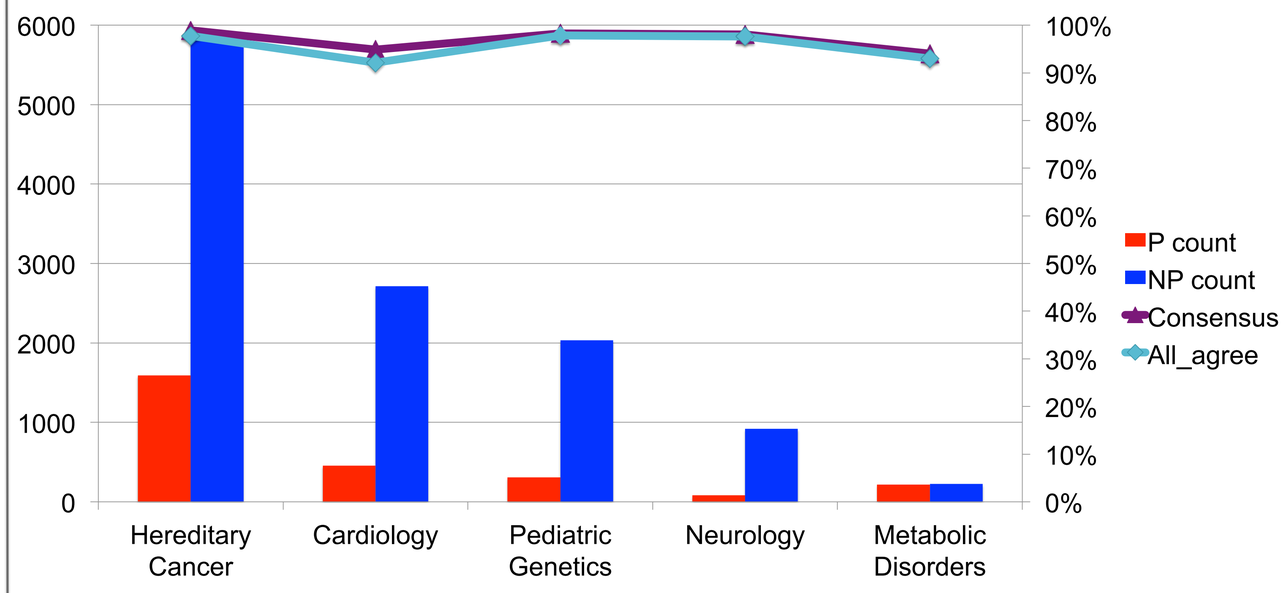
Clinical laboratory concordance rate by disease area

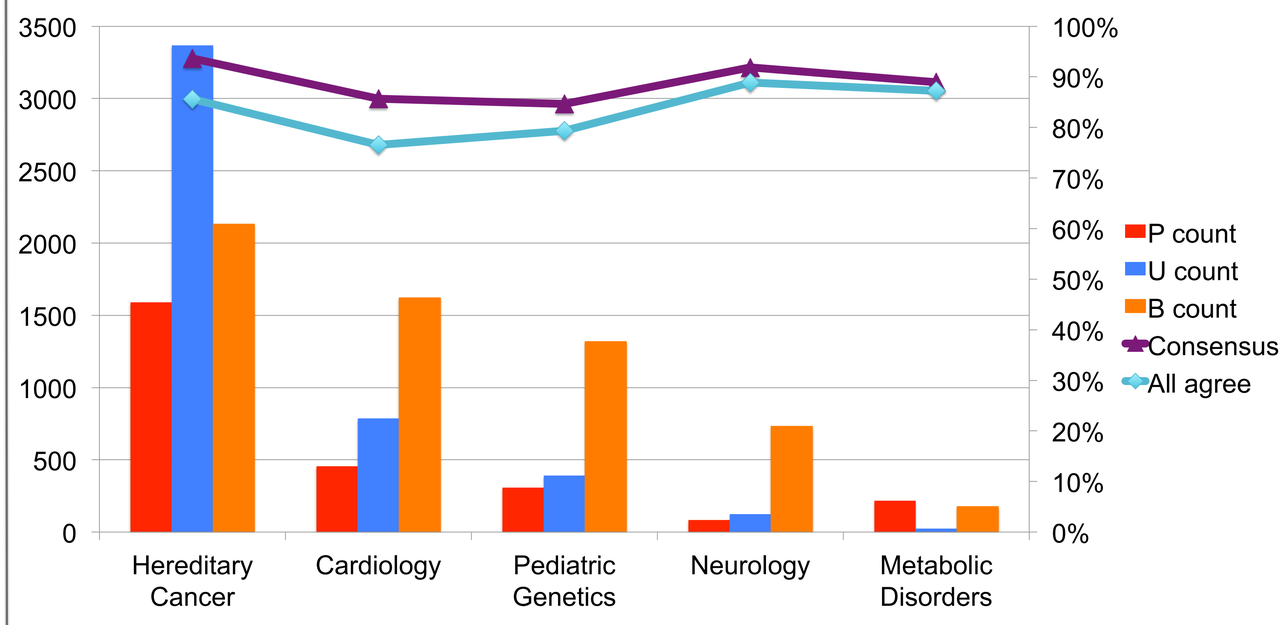
Considering the higher rate of disagreement among literature only, research, and curation submissions, we re-analyzed concordance for submissions from just established clinical testing laboratories (including Myriad Genetics data submitted via SCRP) and limited the analysis to the 974 genes currently offered by Invitae.

- Among 14,802 variants with two or more submissions, 97.65% (14,454) had consensus for clinically actionable (P) and non-actionable (NP) classifications, and 96.32% (14,257) had agreement from all submitters (All_agree).
- Examining consensus by clinical areas revealed the highest agreement for cancer genes (98.89%) and lowest for metabolic disorder genes (94.03%).



When concordance was evaluated and defined with finer detail as P classification versus U and B classifications, the consensus decreased in all clinical areas. This decrease was greater in pediatric genetics and cardiology than in metabolic disorders.

- Variants in cancer, neurology, and inherited metabolic disorder genes maintained approximately 90% consensus concordance.
- Variants of genes in cardiology, pediatric genetics, and hematology genes had a lower concordance of approximately 80%.



Conclusions

In ClinVar, different submitters use different methods to classify variants. Compared with the other main methods, classification using clinical testing is more consistent and has a much lower (5 to 10 fold) frequency of conflicting in P versus NP classifications, which suggests that clinical laboratories that generally follow rigorous guidelines (e.g., ACMG) classify variants consistently with one another.

The major diagnostic laboratories we investigated generally agree on P vs. NP findings. However, classifications of variants in genes in certain disease areas vary in concordance. This disagreement may arise from differences in the depth and sophistication of knowledge about these diseases, the complexity and diversity of genetic causes of these diseases, and the number of laboratories participating in that area in ClinVar, among other reasons.

The small number of differences is important to resolve collaboratively through the peer review of such data, and serves as an key form of laboratory quality control. The learning that results from such comparisons helps improve standards and knowledge among all clinical genetics professionals.