Clinical Laboratories Collaborate to Resolve Variant Interpretation Differences in ClinVar

Steven Harrison – Laboratory for Molecular Medicine
Jill S. Dolinsky – Ambry Genetics
Lisa Vincent - GeneDx
Amy Knight Johnson – University of Chicago
Elizabeth Chao – Ambry Genetics
Danielle Azzariti – Laboratory for Molecular Medicine
Heidi Rehm – Laboratory for Molecular Medicine

Recent efforts by the ClinGen Project to support widespread data sharing using the ClinVar database have allowed clinical laboratories to share variant interpretations that previously had been unpublished or unavailable to the larger community. ACMG recently published guidelines for variant interpretation provide a framework to classify variants; however, given the complexity of variant interpretation, application of guidelines still require subjective interpretation. In addition, some variant interpretations predate these new guidelines. As a result, interpretations differ for 17% of variants in ClinVar with ≥2 submitters. Four clinical laboratories have been working together to resolve differences in their classified variants. As of June 1st 2015, Ambry Genetics, GeneDx, the Laboratory for Molecular Medicine (LMM), and University of Chicago's Genetic Services Laboratory, have shared 9822, 11706, 12092, and 7127 variant interpretations in ClinVar, respectively, resulting in 4879 unique variants interpreted by ≥2 participating labs. Of these variants, 572 (12%) have one- or two-step differences between the three major categories: pathogenic /likely pathogenic, variant of unknown significance, and likely benign/benign. To aid in understanding the basis for differences in interpretation, variant differences were categorized as follows: Differences in Classification Algorithms (e.g. frequency thresholds), Difference in External Evidence (e.g. different data sources used), Differences in Internal Evidence (e.g. proband phenotype or segregation data), and Differences in Subjective Interpretation of Evidence. Identifying reasons for these differences enables the development of more specific guidance for variant interpretation and increases consistency amongst classifications. Preliminary data suggests the reasons for differences are variable, ranging from frequency threshold rules based on variant type and/or mode of inheritance to differences in internal evidence and in interpretation of available evidence. As the four participating clinical labs work through the 572 differences specific to this group, trends are emerging to facilitate resolution of differences in bulk as opposed to evaluating variant-by-variant. Thus, data sharing through ClinVar offers a unique opportunity to identify classification differences between laboratories and to work together to resolve differences and strengthen the interpretation of variants that are used in patient care.

Limit: 2500 characters (including spaces; not including title and authors)
Current: 2491 (not including title and authors)