TRVTHc: a repository compiling variants in treatable human conditions to assist in determining pathogenicity and disseminating treatment-based evidence

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Categories of gene variants
- benign
- likely benign
- variants of uncertain significance (VUS)
- likely pathogenic
- pathogenic

2015 ACMG/AMP guidelines

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

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Limitations and constraints in variant classification

- number of affected individuals identified
- amount of information known regarding a particular gene
  - function
  - protein domains
- *In silico* prediction algorithms
- ability to test affected and unaffected relatives for variant resolution
- functional assay available?

Insufficient molecular evidence leads to a designation of variants of uncertain significance (VUS)

How to improve or add on to the existing criteria?

**Clinical Case** – 2 year old seen for intellectual disability and seizures
Inborn errors of metabolism in which treatment response (“in vivo functional assay”) provided additional evidence of pathogenicity and assisted in variant reclassification

3-phosphoglycerate dehydrogenase (PHGDH) deficiency
lysosomal acid lipase (LAL) deficiency
thymidine kinase 2 (TK2) deficiency
pyridoxamine 5’-phosphate oxidase (PNPO) deficiency
uridine monophosphate synthase (UMPS) deficiency [hereditary orotic aciduria]

Barriers to gathering treatment-based evidence
- information is longitudinal, obtained over time
- time and effort to publish, even for n=1 case reports
- many are (very) rare diseases
- cases only known within an institution, regionally, among a subset of colleagues
- language and geographical constraints

Our goal is for a treatment-driven repository with a low barrier for data entry

This variant database would be a centralized resource to catalogue and disseminate this longitudinal information

Consolidating the collective knowledge and experience will inform and modify future treatment regimens

The Repository for Variants in Treatable Human Conditions
- submitter’s name, contact info, institution
- gene MIM number
- Clingen Allele Registry Canonical Allele Identifier Number
- clinical and laboratory data
- treatment regimen and response, ideally with objective measures

Questions, comments, suggestions? Email: jojshen@ucdavis.edu