

Abstract Title: Increasing diagnostic rate in rare diseases- lessons learnt and defining variants of unknown significance

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Abstract: Mendelian disorders (MDs) are individually infrequent and caused by inherited or de novo or pathogenic changes in a single gene. Advancements in next-generation sequencing (NGS) have provided powerful tools for discovering the genetic basis of MDs and transformed our understanding of the genetic and molecular underpinnings of human development and disease. These new tools have identified therapeutic targets and allowed preclinical diagnosis and mitigation of disease risk. The Yale Center Genome Analysis (YCGA) has been a leader in this effort, sequencing >200,000 exomes, identifying >1,500 novel disease loci for known Mendelian traits, and >800 genes that underlie diseases not previously recognized as Mendelian disorders.

While NGS, especially whole exome Sequencing (WES), has revolutionized the discovery of Mendelian loci, the success in the discovery of causal variants using WES in suspected Mendelian traits is estimated at <50% and the large majority of WES-negative (WES-neg) cases remain unsolved. The high rate of unsolved cases limits the clinical utility of these discoveries, leaving patients and families needing diagnostic answers. Improving the solve rate by systematically defining variants of unknown significance (VUS) as pathogenic, benign, or in between, will significantly impact clinical diagnosis.

Over the past decade, we have developed and implemented cost-effective and innovative genomic and analytical approaches to study and increase the solve rate and discovery of Mendelian diseases. These approaches implement a systematic WES-neg follow-up process utilizing re-analysis by using innovative analytical tools for the interpretation and prioritization of VUS such as whole genome sequencing using short-read and long-read sequencing, RNA sequencing (RNA-seq), methyl-Seq, proteomics, and other integrative 'omics' approaches. We are developing and implementing robust methods to detect and prioritize coding and non-coding variants and assess their functional effect to markedly increase the rate of gene discovery and the clinical solve rate. We are also actively and openly sharing data/metadata with the larger scientific community. These advances will markedly enhance the diagnosis and understanding of genetic diseases, with a broad impact on the treatment of both rare and common human diseases.

Area of expertise: Genetics