Analysis of 5'UTR Variation in Rare Disease Patients Reveals Variants of Potential Disease Relevance

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ABSTRACT IMPACT: This work sheds diagnostic insight on patients with idiopathic rare disease and has the potential to further their care and treatment as a result. OBJECTIVES/GOALS: Correct diagnosis is imperative to treating patients with idiopathic, suspected genetic conditions, yet sequencing approaches leave up to 70% of these patients undiagnosed. We sought to improve diagnosis rates for a cohort patients referred for sequencing by characterizing deleterious variants within the 5'UTR. METHODS/STUDY POPULATION: We retrospectively analyzed whole exome sequencing (WES) data from 472 unsolved rare disease patients within the Mayo Clinic Center for Individualized Medicine to identify variants within the 5'UTR that affect the presence of upstream open reading frames (uORFs). uORFs are short regions (typically 30bp - 600bp) that typically influence downstream gene translation by sequestering ribosomes. We specifically searched for variants with the potential to disrupt existing uORFs or introduce new uORFs within the 5'UTR, and developed a pipeline to annotate these variants with information including GnomAD allele frequency and gene loss of function intolerance (pLI) score. To aid in variant interpretation, we applied two deep learning tools to predict variant impacts on transcript ribosome load (TITER and FramePool). RESULTS/ANTICIPATED RESULTS: Our pipeline identified a median of 21 variants per patient that were predicted to have a deleterious impact on the translational efficiency of protein coding transcripts, primarily by introducing new start codons within the 5'UTR or by altering the Kozak consensus of existing start codons. A median of 10 of these variants occur upstream of haploinsufficient genes with an existing disease association. We also identified a subset of variants that are predicted to introduce translationally active N-terminal extensions to protein coding transcripts, with the potential to disrupt protein localization and processing. DISCUSSION/SIGNIFICANCE OF FINDINGS: This work demonstrates that analysis of 5'UTR variants can be incorporated into existing WES pipelines, and identifies a group of variants with potential significance to patient disease. Further experimental evidence is necessary to ascertain the pathogenicity of these variants.

Clinical Trial

Agreement between point-of-care intestinal ultrasound (POCUS) and magnetic resonance enterography for assessment of the terminal ileum through sigmoid colon in pediatric patients with inflammatory bowel diseases: A diagnostic cross-sectional study

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ABSTRACT IMPACT: Preliminary results will inform the formal evaluation of the reliability of point-of-care ultrasound (POCUS) done by the gastroenterologist compared to standard of care methods such as MR-Enterography. OBJECTIVES/GOALS: Evaluation of mucosal healing is standard for pediatric patients with inflammatory bowel disease (IBD). Point-of-care ultrasound is a non-invasive, cost-efficient tool for assessing intestinal inflammation. We aim to evaluate the agreement between POCUS and typical cross-sectional imaging, such as MR-Enterography (MRE). METHODS/STUDY POPULATION: In this cross-sectional study, we recruited consecutive patients newly diagnosed with IBD, presenting to the specialty outpatient clinic or hospitalized in a pediatric tertiary care center between August to November 2020. They underwent POCUS performed by a single gastroenterologist, in addition to MRE. The sonographer was blinded to MRE results. Bowel wall thickness (BWT) was measured across different bowel segments and recorded twice in longitudinal view and twice in axial view. An average segmental BWT of the four measurements of more than 3 mm was considered inflamed. Agreement between sections of the bowel measured as inflamed were compared to inflamed bowel segments seen by MRE, using Cohen's kappa. RESULTS/ANTICIPATED RESULTS: Eight of 12 patients completed both MRE and POCUS. A total of 40 bowel segments were assessed, namely the terminal ileum, ascending, transverse, descending and sigmoid colon. There were 4 girls with a median age of 15 years (IQR 14.25-16 years), and 6 patients were diagnosed with Crohn's disease. Median PCDAI was 32.5 (IQR 30.6-40), and median PUCAI was 75 (72.5-77.5). Agreement between MRE and point-of-care ultrasound was substantial to perfect for the terminal ileum ******(Î°= 0.75, 95%CI 0.31-1), transverse colon (Î°= 1, 95%CI 1-1) and sigmoid colon (Î°= 1, 95%CI 1-1). The agreement was poor for the ascending (Î°= 0, 95%CI 0-0) and moderate for the descending colon. (Î°= 0.6, 95%CI -0.07-1) DISCUSSION/SIGNIFICANCE OF FINDINGS: In pediatric patients with IBD, we found a high agreement between POCUS and MRE for imaging of the terminal ileum, transverse and sigmoid colon, areas commonly involved in IBD. This reinforces adult data, outlining the potential of POCUS as an evaluation tool of disease activity in clinical practice.

Data Science/Biostatistics/Informatics

Targeted Chemical-Genetic Screen Platform for Identifying Drug Modes-of-Action

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ABSTRACT IMPACT: The key to advancing precision medicine is to deepen our understanding of drug modes-of-action (MOA). This project aims to develop a novel method for predicting MOA of potential drug compounds, providing an experimental and computational platform for more efficient drug discovery. OBJECTIVES/GOALS: To develop (1) a targeted CRISPR-Cas9 chemical-genetic screen approach, and (2) a computational method to predict drug mode-of-action from chemical-genetic interaction profiles. METHODS/STUDY POPULATION: Screening drugs against a gene deletion library can identify knockouts that modulate drug