Dissertation Defense Announcement
To: The George Mason University Community

Candidate: Uma Mudunuri

Program: PhD in Bioinformatics & Computational Biology

Date: Friday, November 17, 2023

Time: 3:00 PM EST

Join Zoom Meeting:

Uma Mudunuri's dissertation defense meeting

Meeting ID: 912 2665 9620
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Committee chair: Dr. Iosif Vaisman
Committee co-chair: Dr. Jack Collins
Committee member: Dr. M. Saleet Jafrij

Title: "Integrated Analysis of Single Nucleotide Variants and Their Functional Annotations for Improved Rare Disease Variant Classifications"

All are invited to attend the defense

ABSTRACT:

Rare diseases impact approximately 1 in 10 Americans and cause a devastating toll on

patients and care givers. A bottom-up approach of analyzing the global variant landscape of rare diseases, especially SNVs, where a single nucleotide change can cause an extreme phenotype, is important for understanding the genes and specific features that lead to rare diseases. As part of this study, SNVs associated with rare diseases and common diseases were analyzed, leading to further in-depth analysis of missense variants that are pathogenic and those that are not associated with a rare disease. Results show that rare disease associated genes tend to be more developmentally lethal. The rarer a disease, the more probable that it's a monogenic disease. In genes where both common and rare disease associated SNVs co-occur, rare disease associated SNVs are more functionally disruptive and the associated protein is either not encoded or when encoded, loses its critical functionality. Our analysis of rare disease and common disease associated SNVs and stratification based on prevalence, lends strength to the fact that diseases should be studied as a spectrum. We show that, in addition to the evolutionary conservation of a site, sequence context and the reference and substituted amino acids contribute heavily to the pathogenicity impact of a missense variant in rare disease associated genes. In this study, we developed custom scores to quantify the functional impact of protein sequence feature overlap and type of amino acid substitution. Random Forest models with the custom scores classified pathogenic and benign variants associated with rare diseases with better prediction accuracies than many popular impact prediction algorithms