THE UNIVERSITY OF BRITISH COLUMBIA

Cellular and Physiological Sciences Seminar Series

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Thursday, February 13, 2020
12:45 - 1:45pm (LSC 3)
Host: Dr. Mark Cembrowski

"Cell types, and the specificity of synaptic connectivity and signaling between them, in primary visual cortex"

As sequencing technologies become more economical, we are identifying sequence variations in the population faster than ever. For disease-associated genes, it is imperative that we can differentiate a sequence variant as either benign or pathogenic such that the appropriate therapeutic interventions or surveillance can be implemented. PTEN (Phosphatase and TENsin homolog) is a frequently mutated tumor suppressor that has been linked to the PTEN hamartoma tumor syndrome. While the domain structure of PTEN and the functional impact of a number of its most common tumor-linked mutations have been characterized, there is a lack of information about many recently identified clinical variants. To address this challenge, we developed a cell-based assay that utilized a premalignant phenotype of normal mammary epithelial cells lacking PTEN. We measured the ability of PTEN variants to rescue the spheroid formation phenotype of PTEN-/- MCF10A cells maintained in suspension. As a proof of concept, we functionalized 47 missense variants using this assay, only 18 of which have clear classifications in ClinVar. We utilized a machine learning model trained with annotated genotypic data to classify the variants as benign or pathogenic based on our functional scores. Our model predicted with high accuracy that loss of PTEN function was indicative of pathogenicity. We also determined that the pathogenicity of certain variants may have arisen from reduced stability of the protein product. Overall, this assay outperformed computational predictions, was scalable and had a short run time and could be an ideal alternative for annotating the clinical significance of cancer-associated PTEN variants.

Join us for coffee and cookies at 12:15 in LSC 1416
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