Stony Brook University
The Graduate School

Doctoral Defense Announcement

Abstract

Toward Precision Medicine: From Clinical Genomics to Induced Pluripotent Stem Cell Disease Modeling

By

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The ability to unveil the genetic landscape of human disease at an extraordinarily detailed resolution through high-throughput DNA sequencing promises a transformation of medical practice toward precision medicine. However, it is not a straight path from producing individual genomics data to pinpointing the disease-contributory variants and delivering the personalized therapy, due to the complexity of human genome architecture, genotype-phenotype correlation and disease pathogenesis. But first and foremost for precision medicine to succeed is to ensure the reliability and accuracy of the generation and interpretation of clinical genomics. Indeed, the rapidly growing diversity of DNA sequencing platforms, protocols and variant detection algorithms has enabled researchers and clinical investigators to choose the most cost-effective method based on their own needs and interest. However, due to a lack of a high-throughput validation protocol, the reliability of each method and the comparability among them has yet to be characterized. Meanwhile, a comprehensive investigation of the clinical findings must be equally executed in order to achieve a better design of sequencing projects and prioritization of disease-associated variants, especially for patients presenting a complex history. However, the hurdles to obtaining first-hand clinical data and a lack of standardized vocabulary use in medical documentation have prohibited this information from being utilized to its maximum potential. Furthermore, before any therapeutics can be developed, a robust disease model needs to be constructed to prove the causality of the pinpointed variants and understand the functional impact of it in disease affected cell types or tissues. This dissertation research aimed to address the above key issues, and introduced a successful example of applying these advancements to the discovery of TAF1 syndrome. Moreover, it also illustrated the challenge and opportunity of utilizing patient induced pluripotent stem cell-derived cardiomyocytes as a model to investigate the functional impact of Naa10 S37P variant in the pathogenesis of cardiac dysrhythmias in Ogden syndrome.

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