Researchers develop platform to identify cancer mutations that may be responsive to drug therapies

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A Cleveland Clinic-led team of researchers has developed a personalized genomic medicine platform that will help advance accelerate genomic medicine research and genome-informed drug discovery, according to new study results published recently in Genome Biology.

Known as My Personal Mutanome (MPM), the platform features an interactive database that provides insight into the role of disease-associated mutations in cancer and prioritizes mutations that may be responsive to drug therapies.

"Although advances in sequencing technology have bestowed a wealth of cancer genomic data, the capabilities to bridge the translational gap between large-scale genomic studies and clinical decision making were lacking," said Feixiong Cheng, Ph.D., assistant staff in Cleveland Clinic's Genomic Medicine Institute, and the study's lead author. "MPM is a powerful tool that will aid in the identification of novel functional mutations/genes, drug targets and biomarkers for cancer, thus accelerating the progress towards cancer precision medicine."

Using clinical data, the researchers integrated nearly 500,000 mutations from over 10,800 tumor exomes (the protein-coding part of the genome) across 33 cancer types to develop the comprehensive cancer mutation database. They then systematically mapped the mutations to over 94,500 protein-protein interactions (PPIs) and over 311,000 functional protein sites (where proteins physically bind with one another) and incorporated patient survival and drug response data.

The platform analyzes the relationships between genetic mutations, proteins, PPIs, protein functional sites and drugs to help users easily search for clinically actionable mutations. The MPM database features three interactive visualization tools that provide two- and three- dimensional views of disease-associated mutations and their associated survival and drug responses.

The results from another study published in *Nature Genetics*, a collaboration between Cleveland Clinic and several other institutions, motivated the team to develop the platform.

Previous studies have linked disease pathogenesis and progression to mutations/variations that disrupt the human interactome, the complex network of proteins and PPIs that influence cellular function. Mutations can disrupt the network by changing the normal function of a protein (nodetic effect) or by altering PPIs (edgetic effect).

Notably, in the *Nature Genetics* study, led by Brigham & Women's Hospital and Harvard Medical School, the researchers found that disease-associated mutations were highly enriched where

PPIs occurred. They also demonstrated PPI-altering mutations to be significantly correlated with drug sensitivity or resistance as well as poor survival rate in cancer patients.

Collectively, MPM enables better understanding of mutations at the human interactome network level, which may lead to new insights in cancer genomics and treatments and ultimately help realize the goal of personalized care for cancer. The team will update MPM annually to provide researchers and physicians the most complete data available.

"Our *Nature Genetics* study also demonstrates the effects of mutations/variations in other diseases," added Dr. Cheng. "As a next step, we are developing new artificial intelligence algorithms to translate these genomic medicine findings into human genome-informed drug target identification and precision medicine drug discovery for other complex diseases, including heart disease and Alzheimer's disease."

More information: Yadi Zhou et al, My personal mutanome: a computational genomic medicine platform for searching network perturbing alleles linking genotype to phenotype, *Genome Biology* (2021). DOI: 10.1186/s13059-021-02269-3

Cheng, F., Zhao, J., Wang, Y. et al. Comprehensive characterization of protein–protein interactions perturbed by disease mutations. Nat Genet (2021). doi.org/10.1038/s41588-020-00774-y , www.nature.com/articles/s41588-020-00774-y

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