conferenceseries.com

Joint meet on 13th International Conference on PREDICTIVE, PREVENTIVE AND PERSONALIZED MEDICINE & MOLECULAR DIAGNOSTICS.

July 27, 2021 | Webinar

# Identify non-mutational TP53 loss of function in human cancers

**Liguo Wang**
*United States*

Disruption of gene function is not solely caused by genetic alteration in cancer. A gene with an intact DNA sequence can also compromise its function by epigenomic, transcriptomic, and proteomic level dysregulations (i.e., non-mutational inactivations). Non-mutational inactivations are prevalent in cancers but, due to the heterogenetic causes, cannot be detected by the DNA-sequencing, immunohistochemical staining or any other single assay alone. Therefore, they would become a significant impediment for molecular diagnostics, clinical management, and treatment selection for cancer patients. We hypothesized that when TP53 is functionally impaired, either due to genetic or non-genetic causes, the expression of downstream target genes would be significantly altered, and that such expression alteration, in turn, can be used to predict the status (i.e., normal or loss-of-function/LoF) of TP53. To identify non-mutational inactivations of p53, we first define p53 target genes through a comprehensive literature review and meta-analysis. Then, we build an SVM model using the composite expression scores of these target genes as features, and using the “non-cancerous normal tissues” (assuming p53’s tumor suppressor function is normal in this group) and “TP53truncating tumor samples” (assuming p53’s tumor suppressor function is lost in this group) as training datasets.

**Results:** Using 5-fold cross-validation, we demonstrated the superior performance of our SVM models (average AUC = 0.995, F1-score = 0.989, recall = 0.992) in TCGA LUNG and BRCA cohorts. When applying our SVM model to TP53WT tumor samples, we found 87% of BRCA and 94% of LUNG samples were predicted to be LoF (termed as TP53WT-LoF). These TP53WT-LoF patients exhibited distinct genomic and clinical characteristics from the other TP53WT patients. Specifically, TP53WT-LoF patients have significantly higher tumor mutation burden, fraction of genome with copy number variations, aneuploidy score and hypoxia score, consistent with p53’s function as a central regulator of DNA damage repair and cellular stress response. In addition, TP53WT-LoF patients with lung cancer have significantly shortened overall survival, compared to those real TP53WT patients. Further analyses revealed that MDM2/MDM4 amplifications are significantly enriched in TP53WT-LoF patients, partially and mechanistically explained the p53 loss-of-function.

## Biography

Dr. Liguo Wang is a Researcher in Division of Computational Biology, Department of Quantitative Health Sciences□Mayo Clinic. High-throughput technology such as DNA sequencing could produce massive data from clinical samples. The research of Liguo Wang, Ph.D., concentrates on developing computational tools and methods to transform big data into biological insights and provide cognitive support for data-informed clinical decision-making and precision medicine.

Wang.Liguo@mayo.edu