JOHNS HOPKINS BLOOMBERG SCHOOL of PUBLIC HEALTH

Department of Biostatistics

BIOSTATISTICS SEMINAR

Analyzing Mutual Exclusivity of Somatic Mutations in Tumor Sequencing Studies

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Abstract:

The central challenge in tumor sequencing studies is to identify driver genes and pathways, investigate their functional relationships and nominate drug targets. The efficiency of these analyses, particularly for infrequently mutated genes, is compromised when subjects carry different combinations of driver mutations. Mutual exclusivity analysis helps address these challenges. To identify mutually exclusive gene sets (MEGS), we developed a powerful and flexible analytic framework based on a likelihood ratio test and a model selection procedure. Extensive simulations demonstrated that our method outperformed existing methods for both statistical power and the capability of identifying the exact MEGS, particularly for highly imbalanced MEGS. Our method can be used for *de novo* discovery, pathway-guided searches or for expanding established small MEGS. We applied our method to the whole exome sequencing data for thirteen cancer types from The Cancer Genome Atlas (TCGA). We identified multiple previously unreported non-pairwise MEGS in multiple cancer types. For acute myeloid leukemia, we identified a MEGS with five genes (*FLT3*, *IDH2*, *NRAS*, *KIT* and *TP53*) and a MEGS (*NPM1*, *TP53* and *RUX1*) whose mutation status was strongly associated with survival (P=6.7×10^{-4}). For breast cancer, we identified a significant MEGS consisting of *TP53* and four infrequently mutated genes (*ARID1A*, *AKT1*, *MED23* and *TBL1XR1*), providing support for their role as cancer drivers. Algorithms are implemented in an R package MEGSA.

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