Study IDs Recurrent Mesothelioma Tumor Alterations

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NEW YORK (GenomeWeb) – In a new paper published today in Nature Genetics, researchers from the US and India described the mutation patterns and recurrent alterations they detected in malignant pleural mesothelioma.

Using whole-exome, targeted exome, and/or transcriptome sequence data for 216 malignant pleural mesothelioma tumors, the Brigham and Women's Hospital- and Genentech-led team narrowed in on genes and pathways with recurrent alterations in the rare but aggressive lung cancer, detecting a few potential treatment targets.

"[W]e've been able to describe a spectrum of mutations for this rare disease," co-first author Raphael Bueno, chief of Brigham and Women's Hospital's thoracic surgery division and co-director of the hospital's lung center, said in a statement. "A small number of these mutations have been found previously in other cancers, and drugs have been developed to target these mutations. No one knew before now that these mutations might also be found in mesothelioma tumors."

Although rare, mesothelioma cases are typically aggressive, the team explained, and malignant pleural mesothelioma accounts for an estimated 3,000 deaths per year in the US. Asbestos exposure has been implicated in roughly 80 percent of mesothelioma cases, while other cases are typically attributed to genetic predisposition, chest radiation, or spontaneous changes arising in mesothelial cells.

To explore molecular features present in mesothelioma, the researchers got access to matched tumor and normal samples from 216 individuals with malignant pleural mesothelioma. They assessed all but five of the tumors with RNA sequencing, using the Illumina HiSeq 2500.

The team also did targeted sequencing on 103 tumors — focusing on 344 genes in the Ovation Cancer Panel kit — and whole-exome sequencing on 99 tumors, again using Illumina HiSeq 2500 instruments. Whole-genome sequencing to an average coverage of around 100-fold was done at Complete Genomics for 20 of the samples.

The tumors fell into four transcriptional clusters known as sarcomatoid, epithelioid, biphasic-sarcomatoid (biphasic-S), and biphasic-epithelioid (biphasic-E), researchers reported. Of these, the sarcomatoid tumor subtype was prone to enhanced expression of the PD-L1 immune checkpoint gene, suggesting it might be susceptible to immunotherapy-based treatment. All told, the researchers found that more than one-third of the tumors profiled by RNA sequencing were PD-L1-positive.

The researchers found other potential treatment clues when they scrutinized gene splicing patterns in the RNA-seq data, uncovering tumor samples with ABL1 gene splicing alterations expected to activate the resulting kinase.

When they sifted through more than 2,500 somatic mutations expected to alter the resulting protein sequences, meanwhile, comparing them with mutations in the COSMIC database and MedGenome's OncoMD, the investigators detected 10 significantly mutated genes, including genes coding for protein kinase enzyme and chromatin modifier pathway components.

Alterations in several of the same genes turned up when they profiled copy number patterns in 95 malignant pleural mesothelioma tumors with the help of genome-wide sequence and/or Illumina SNP array data, while an integrated analysis pointed to the involvement of additional pathways in mesothelioma.

The team noted that nearly two-dozen of the tumors contained at least one gene fusion. In contrast to prior analyses highlighting the role of activating oncogene fusions in cancer, the mesothelioma tumor set harbored examples of inactivating fusions affecting tumor suppressor genes. The most frequently mutated malignant pleural mesothelioma genes — SF3B1 and TRAF7 — each contained glitches in about 2 percent of the tumors.

"When you have a cancer that has a[n] 80 to 90 percent mortality rate within five years of diagnosis, and you discover evidence that a small percentage of people may have actionable mutations, that means that you could reduce mortality," Bueno said in a statement. "Even for a mutation that happens one to two percent of the time, it could mean the difference between life and death for a patient."