Bioinformatics Boosts Cancer Research

Biomedical informatics is changing our understanding of the management of cancer. That was recently illustrated when a team of Yale Cancer Center scientists used molecular genomic and computational biology to reveal novel information about melanoma.

The team analyzed skin cancer data from 233 melanoma patients, the second largest such sequencing effort ever done. "We were looking for a better understanding of all the types of mutations that must happen for melanoma to occur," said Michael Kravtshuk, MD, PhD, Associate Pathology.

They found several surprises. Scientists already knew that some melanomas depend on mutations in either the BRAF gene (about 50 percent) or the NRAS gene (10 to 30 percent), but the mutations that caused the remaining 20 to 30 percent were unknown. Researchers discovered that some melanomas contain mutations in the BRAF gene, but NRAS's role isn't well defined.

The same gene, called as part of the Ras family in Skin Cancer, showed that mutations of NRAS account for 10 to 15 percent of melanomas, making them the third most important driver of the cancer. Further, NRAS mutates help activate the MAPK pathway, the same one triggered by epidermal growth factor receptor (EGFR) mutations in patients with an NF1 mutation melanoma into a much better understood category," explained Dr. Kravtshuk, "particularly because it's acting on a pathway for which we already have multiple drugs available. We didn't have this knowledge before.

There were other surprises. First, the genome of NF1 patients was much more related than those of other melanoma patients. Second, patients in the NF1 subgroup were also much older. "That puzzled us," said Dr. Kravtshuk. "Why would they have so many more mutations—thousands of them—and be older?" The researchers noticed that NF1 mutations didn't seem to be strong activators of MAPK. "This lack of the activating hypophosphorylation that might occur in these melanomas have to reside in the body long and acquire more mutations to become as active and malignant as a BRAF or NRAS melanoma."

The researchers then discovered that the NF1 melanomas were acquiring additional mutations from a parallel disease, Rasopathy. Rasopathies are developmental disorders such as Noonan syndrome and Neurofibromatosis, caused by germline (inherited) genetic mutations, as distinct from somatic mutations in cancer, which happen after conception and can't be inherited. Rasopathies were not known to be related to melanomas, but they do activate the MAPK pathway—a common one used by NF1. Dr. Kravtshuk and his team found that the mutations in Rasopathies were identical to those in most NF1. Further analysis suggested that NF1 mutations by themselves are too weak to cause melanoma, but when joined with Rasopathy mutations, the combination may activate the MAPK pathway for melanoma.

These findings begin with the analysis of 20,000 genes in 100 melanomas—still a sizable number. "Melanoma has so many more mutations than other cancers," said Dr. Kravtshuk, "but we were able to identify a key subset of genes that we are going to sequence a large cohort of melanoma patients that are treated at Yale. That will give us a big hint about what's going on in response to the targeted therapies already in use against melanoma, or possibly to the new immunotherapies."

The fact that so many mutated genes are implicated in melanoma is changing our understanding of cancer. "Strikingly, it’s less about whether a disease is a developmental delay, or a skin cancer, or a blood cancer," he added, "and more about the underlying molecular mechanism. That’s why bioinformatics is so useful in modern cancer research —it’s a way to go beyond the usual molecular."

Cancer Genomics, Genetics, and Epigenetics RESEARCH PROGRAM

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