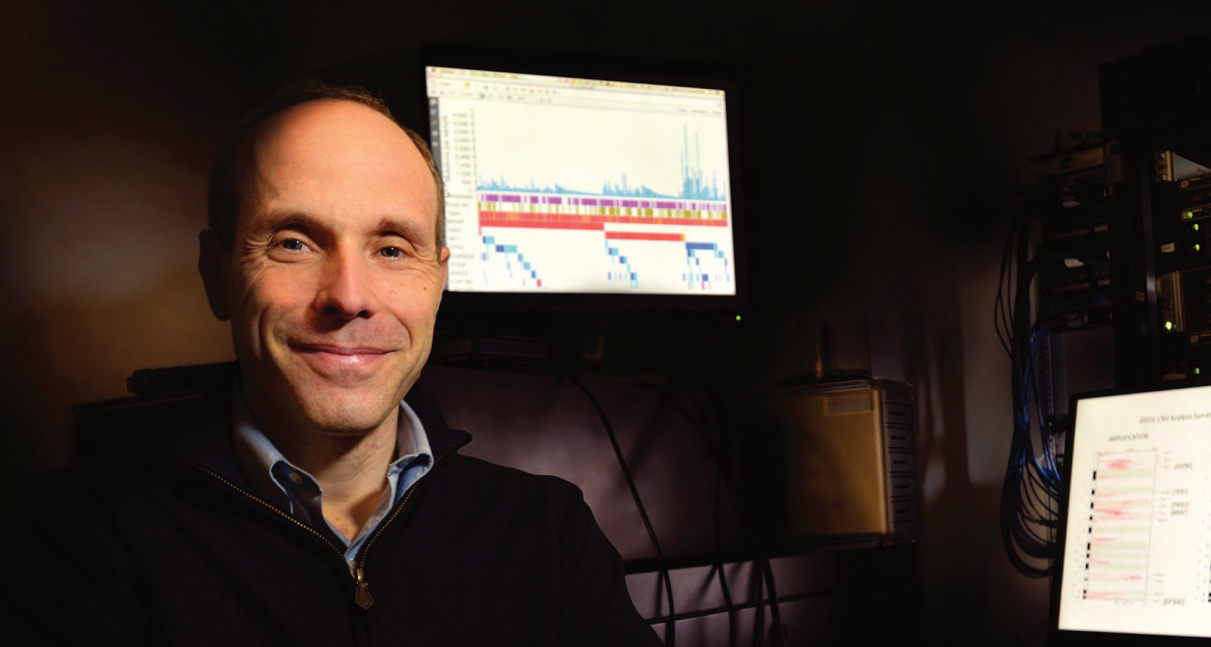

Michael Krauthammer, MD, PhD

Bioinformatics Boosts Cancer Research

Biomedical informatics is changing our understanding and treatment of cancer. That was recently illustrated when a team of Yale Cancer Center scientists used molecular sequencing and computational biology to reveal startling new information about melanoma.

The team analyzed exome data from 213 melanoma patients, the second largest such screening ever done. "We were looking for a better understanding of all the types of mutations that must happen for melanoma to occur," said Michael Krauthammer, MD, PhD, Associate Professor of Pathology.

They found several surprises. Scientists already knew that most melanomas stem from mutations in either the BRAF gene (about 50 percent) or the NRAS gene (20 to 30 percent), but the mutations that caused the remaining 20 to 30 percent were unclear. Researchers did know that some melanomas contained mutations in the NF1 gene, but NF1's role wasn't well defined.

The Yale screen, conducted as part of the Yale SPORE in Skin Cancer, showed that mutations of NF1 account for 10 to 15 percent of melanomas, making them the third most important driver of the cancer. Further, NF1 mutations help activate the MAPK pathway, the same one activated by oncogenic mutations in BRAF and NRAS.

"This moves patients with an NF1 mutant melanoma into a much better understood category," explained Dr. Krauthammer, "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 mutated than those of other melanoma patients. Second, patients in the NF1 subgroup were also much older.

"That puzzled us," said Dr. Krauthammer. "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. "That led to the interesting hypothesis that maybe these NF1 melanomas have to reside in the body longer and acquire more mutations to become as active and malignant as a BRAF or NRAF melanoma."

The research team discovered that NF1 melanomas were acquiring additional mutations from a parallel disease, RASopathies. 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 melanoma, but they do activate the MAPK pathway – the same one used by NF1. Dr. Krauthammer and his team found that the mutations in RASopathies were identical to those in mutated 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 began with the analysis of 20,000 genes for the mutations most important to melanoma. They have narrowed the list to about 100 genes – still a sizable number. "Melanoma has so many more mutations than other cancers," said Dr. Krauthammer, "but we were able to identify a key subset of genes that we are going to sequence across a large cohort of melanoma patients that are treated at Yale. That will give us a big hint about what his or her response will be 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 altering our understanding of cancer. "Suddenly 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 – to analyze a lot of data, recognize patterns, and establish links to mutations in other diseases."