Researchers at Yale Cancer Center are using powerful DNA sequencing machines to map genetic landscapes and locate the mutations that cause cancer. Melanoma, one of the most common and deadly cancers, is a priority. 

In 2012 Ruth Halaban, PhD, Senior Research Scientist in Dermatology, and her collaborators sequenced the exomes of 147 melanomas, the largest sequencing project ever done on the disease. They were looking for recurring mutations—that is, mutations that change a protein at exactly the same place again and again.

The scientists discovered several recurring mutations that were previously unknown. One of them was responsible for about 9 percent of sun-exposed melanomas—an mutation in a gene called RAC1. In every instance, the mutation occurred when a single amino acid was replaced by another. That was all it took to lock the gene’s signal permanently on, which enhanced normal cells to multiply and disperse.

“The percentage of melanomas produced by this mutation may not look like a lot, but it’s the third most common mutation behind the BRAF and NRAS genes, and it hadn’t been described before.”

Pinpointing the gene and the mutation gives researchers a clearer target for designing a therapy specific to this cause of melanoma. Melanoma patients with a faulty BRAF gene, for instance, are now treated with vemurafenib, a new drug targeting that mutation. Dr. Halaban hopes that something similar will be developed for RAC1 as cancer treatment becomes more personalized.

Equally important, the researchers discovered that the RAC1 mutation is triggered by UV radiation, the first time a direct link has been shown between a frequently sun-damaged gene and melanoma. The BRAF and NRAS mutations, though known to be implicated in melanoma, don’t show the signature of UV damage. Dr. Halaban and her colleagues, by contrast, found UV damage on the mutated RAC1 gene—clear evidence that UV radiation alters the gene, which then drives toward malignancy.

In a healthy body, the pigment cells that regulate skin pigmentation are kept relatively immobile in the skin. But when RAC1 mutates, the pigment cells not only begin to divide faster, they escape their environment and migrate out to distant sites.

“That’s a bad sign,” said Dr. Halaban. “The RAC1 mutation is the gas that accelerates the car, and it won’t shut off, which causes cell proliferation and migration that leads to melanoma.”

Dr. Halaban pointed out that none of these new findings would have been possible a decade ago, before high-speed sequencing. “You also need money to run the samples,” she said, “people who know how to operate the machines, surgeons and clinicians to give you tissue specimens, experts in bioinformatics and biostatistics to analyze those millions of data points and tell you what’s there, and basic scientists to interpret the results and validate the function of the mutant protein. The whole collaboration at Yale is amazing.”

As another example of this advantage, she points to the Yale SPORE (Specialized Programs of Research Excellence) in Skin Cancer, a multidisciplinary research program that she directs as principal investigator. The program’s funding by the National Cancer Institute was renewed in August for another five years and $11.5 million.

“The SPORE created a community of investigators and clinicians that otherwise wouldn’t have the opportunity or funding to relate their talents to melanoma.”

Dr. Halaban explained. “Before the SPORE, two or three people here worked on melanoma. Now we have about 80 working on several major projects related to this cancer.”