# UCSF Team Studying Genomics of Rare Cancers With Geographic Hotspots

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SAN FRANCISCO (GenomeWeb) – A research team at the University of California, San Francisco aims to study cancer genomes from tumor types that are globally rare but have geographic hotspots where incidence rates soar.

As a first part of such work, the team has sequenced the whole genomes and transcriptomes of 61 esophageal tumors from patients in Tanzania.

The UCSF team has been collaborating with Muhimbili University of Health and Allied Sciences and the Ocean Road Cancer Institute in Dar es Salaam, Tanzania for the project, which is part of UCSF's Global Cancer Program launched this fall. In addition, NantWorks donated sequencing services.

Katherine Van Loon, a gastrointestinal oncologist and director of the Global Cancer Program, said she had been working in Tanzania for much of the last decade on cancer epidemiology when her team realized that a corridor along the eastern coast of Africa had a very high incidence of esophageal cancer, which is one of the less common cancers in much of the rest of the world. It is the second most common cancer for men and the third most common for women. In addition, nearly 15 percent to 20 percent of those affected are people under the age of 40, "which is really striking," she said.

"Anytime you see a geographic pocket of cancer, that points to a genetic or environmental risk factor or some interaction between the two that makes a population particularly susceptible," she said.

Using genomics to study such hotspots can help shed light on the disease etiology and uncover genetic risk factors that may be specific to the population or identify known or novel mutagenic signatures that point to an environmental cause. That information can be used to understand how esophageal cancer may present differently in different populations, inform diagnosis and management of those patients, and provide a broader understanding of the disease.

Van Loon said that a key first step of the study was to put in place the infrastructure. The researchers set up a tumor repository at UCSF, she said, but one challenge was to figure out how to cost-effectively transport samples from Tanzania to UCSF without damaging them. In addition, she said, the researchers wanted to put in place infrastructure locally in Tanzania to ensure that the work would be sustainable.

Van Loon said that the team designed a novel transport process by which samples could be shipped at room temperature without sacrificing DNA and RNA quality. She declined to disclose details of the method because the researchers plan to submit it to a peer-reviewed journal but she said that essentially, RNA is "used as a room-temperature transport medium."

In addition, she said that the team has attempted to be mindful of cultural differences and its responsibility to ensure that the local community sees some benefit from the research.

"There's lots of opportunities to criticize scientists for going to Africa and taking specimens out of the country," she said, so the team has worked hard to ensure that it shares knowledge from the study and works with local scientists to establish infrastructure and protocols to enable the research to continue within the country.

To that end, the UCSF team has partnered with Muhimbili University of Health and Allied Sciences to train and mentor scientists.

As for the initial tumor sequencing project, Van Loon said that the researchers are continuing to analyze the sequence data, but that there have been a few interesting preliminary findings.

The prevalence of TP53 mutations was one area the researchers wanted to focus on because TP53 mutations are found in nearly every case of esophageal cancer in US populations. However, a study published last year in JCI Insight of a cohort of Malawian patients with esophageal cancer found that although TP53 was still altered in around 60 percent of the cohort, in other populations the gene is mutated in more than 90 percent of patients, Van Loon said.

As such, the team was curious to see whether the TP53 mutation rate in the Tanzanian patients matched that of the Malawian cohort. While an initial analysis indicated that the mutation rate may be similar, she said that on a deeper analysis, the team found additional TP53 mutations that it had missed, which she hypothesized was due to low sequence coverage.

Similar to the Malawian dataset, the data from Tanzania did not uncover the mutational signature associated with tobacco, which is a known risk factor for esophageal cancer — not surprising given that most esophageal cancer patients in eastern Africa are nonsmokers, she said.

The team is continuing to analyze the data, however, to look for mutational signatures that could be associated with other environmental exposures. For instance, ultraviolet radiation leaves a distinct mutagenic signature in melanoma tumor genomes and smoking leaves a distinct mutagenic signature in lung cancer genomes. For esophageal cancer, there has been some evidence that drinking extremely hot beverages could be a risk factor, she said. The team is also looking into other risk factors, such as ventilation around cooking or ways in which grains are preserved, and the processes and ingredients involved in local brews.

"In one of our studies, we found that women are cooking indoors without any ventilation, so whole families are being affected by smoke inhalation," she said. That's not been verified as a cause of esophageal cancer yet, but she said it's one aspect the team would look into.

Eric Collisson, a medical oncologist at UCSF, is spearheading much of the data analysis looking for mutational signatures. One first step will be to look for the known mutational signatures, of which he said there are around 20. Different types of cancers and tumor types tend to have a different distribution of mutational signatures, he said. So, the researchers will first look to see how the set of Tanzanian tumors fit within the known distribution for other esophageal cancers. If there is a significant difference between the Tanzania dataset and datasets from other cohorts, that will be the first clue, he said.

Van Loon said that the team is also collaborating with experts in pathogen discovery to see whether an infectious agent may play a role in the etiology of esophageal cancers in the

region. Human papillomavirus for instance, is known to lead to cervical cancer, but she said it doesn't seem to cause esophageal cancer, "so that's not high on our list of hypotheses, but we're taking a very broad approach."

She said she also plans to compare the Tanzanian dataset with that from the Malawian cohort to look for similarities and differences.

In addition, a key focus will be to figure out whether there are any biomarkers that could be used to improve diagnostics. Currently, most patients are diagnosed at late stages, Van Loon said. A better understanding of the genomic landscape and risk factors for getting the disease could enable better screening methods. "Figuring out an early cancer strategy for a high-risk population is critical," she said.

The sequence data has also been deposited into dbGaP, so others can analyze it. That will be important, she said, because the Cancer Genome Atlas project did not include populations from Africa.

Collisson added that the researchers will be comparing the dataset to the TCGA datasets to see "where it fits on this continuum of different human cancers."

In addition, he said, the UCSF team plans to study other cancers that have high incidence rates in certain geographic areas, but that are overall relatively rare. The goal is to "understand why certain areas have a high enrichment of relatively rare cancers," he said. For instance, one potential next step will be to look at gall bladder cancer in certain parts of Chile.