

Scientists use genome sequencing to prove herbal remedy causes upper urinary tract cancers

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Genomic sequencing experts at Johns Hopkins partnered with pharmacologists at Stony Brook University to reveal a striking mutational signature of upper urinary tract cancers caused by aristolochic acid, a plant compound contained in herbal remedies used for thousands of years to treat a variety of ailments such as arthritis, gout and inflammation. Their discovery is described in the Aug. 7 issue of *Science Translational Medicine*.

Aristolochic [pronounced a-ris-to-lo-kik] acid is found in the plant family "Aristolochia," a vine known widely as birthwort, and while the U.S. Food and Drug Administration first warned of its cancer-causing potential in 2001, botanical products and herbal remedies containing it can still be purchased online. Moreover, the vine has been found to be an environmental carcinogen through the contamination of food supplies of farming villages in the Balkans, where Aristolochia grows wildly in the local wheat fields. For years, scientists have known of some mutations in upper [urinary tract cancer](#) patients exposed to the plant toxin. But the genome-wide spectrum of mutations associated with aristolochic acid exposure remained largely unknown.

For the current study, the Johns Hopkins and Stony Brook team used whole-exome sequencing on 19 Taiwanese upper [urinary tract cancer patients](#) exposed to aristolochic acid, and seven patients with no suspected exposure to the toxin. The technique scours the exome, part of

the human genome that contains codes for [functional proteins](#) and can reveal particular mutations, in this case, those associated with cancer.

"Genome-wide sequencing has allowed us to tie aristolochic acid exposure directly to an individual getting cancer," Kenneth Kinzler, Ph.D., professor of oncology in the Johns Hopkins Kimmel Cancer Center's Ludwig Center for Cancer Genetics and Therapeutics. "The technology gives us the recognizable mutational signature to say with certainty that a specific toxin is responsible for causing a specific cancer. Our hope is that using the more targeted whole-exome-sequencing process will provide the necessary data to guide public health decisions related to cancer prevention."

Specifically, Kinzler says they found an average of 753 mutations in each tumor from the toxin-exposed group compared with 91 in tumors from the non-exposed group. This level of mutation is more than that found in melanomas caused by ultraviolet radiation and lung cancer caused by smoking.

The toxin-exposed group had a large number of a particular, rare type of mistake (a mutational signature) in the ATCG chemical code of their DNA. The predominant mutation type in the toxin-exposed tumors (72 percent) was an A substituted with a T. In one instance, the scientists used the mutational signature to uncover an aristolochic-related tumor in a patient who was unaware of prior exposure.

This study illustrates how genomic sequencing could also be used to pinpoint a culprit carcinogen in some cancer clusters, says Margaret L. Hoang, Ph.D., lead author of the study. Cancer clusters are defined as an unusually large number of similar cancers occurring within a specific group of people, geographic area or period of time.

More information: "Genome-Wide Mutational Signatures of

Aristolochic Acid and Its Application as a Screening Tool," by S.L. Poon et al *Science Translational Medicine*, 2013.

Provided by Johns Hopkins University School of Medicine

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