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## Scientists Discover Gene Mutation Common in a Class of Ovarian Cancers

A study of aggressive ovarian tumors has revealed a new class of major cancer-driving mutations. Howard Hughes Medical Institute (HHMI) researchers found that most of the clear cell ovarian carcinoma samples they studied carried a gene mutation that alters the epigenetics of cells.

The mutations may disrupt chemical and structural modifications to histone proteins – part of the protein-DNA structure called chromatin that helps determine whether genes are activated or silenced.

Cancer cells frequently show evidence of severe epigenetic disruptions, but scientists have known very little about how these disruptions occur, or how important they are in driving cancer. The new study, published online in *ScienceExpress* on September 8, 2010, is the first to suggest that mutations in a chromatin-modifying gene occur in the majority of cases of any form of cancer.

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- Bert Vogelstein

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The study's senior authors, HHMI investigator Bert Vogelstein and colleagues Luis A. Diaz, Jr., Kenneth W. Kinzler, Victor E. Velculescu, and Nickolas Papadopoulos, are based at the Ludwig Center for Cancer Genetics and Therapeutics at Johns Hopkins University's School of Medicine.

In the present study, the researchers surveyed the mutations underlying clear cell ovarian carcinoma, the most treatment-resistant type of ovarian cancer. As with other cancer cells, clear cell ovarian carcinoma cells become cancerous only after acquiring a series of mutations to key genes – mutations that may have been inherited, but more often are caused by chemicals or

radiation or random molecular mishaps during cell division. Recent advances in DNA-sequencing technology have made it possible to catalog such mutations more quickly than ever.

In tumor cells taken from patients with ovarian clear cell carcinoma, the team sifted through all 18,000 or so protein-encoding genes. They found that in a typical patient, nearly two dozen of these genes were mutated in the tumor cells, but were not mutated in the patient's non-cancerous cells. Most of these tumor-linked mutations were rare, appearing only in one patient's tumor. But the analysis also revealed four genes that were mutated more commonly.

By far the most common of these mutant genes, *ARID1A*, appeared in 57 percent of the samples. The mutations in *ARID1A* were completely unexpected, although other cancers were known to involve the disruption of large stretches of DNA that included *ARID1A*.

"The frequency of these *ARID1A* mutations in the ovarian tumor samples drew our attention because the gene is involved in determining the epigenetics of cells," says Vogelstein.

Epigenetics is a burgeoning research field that explores inherited changes in gene activity that do not involve alterations in the primary DNA sequence. During growth and development, genes that should not be expressed are physically tagged with chemicals, such as methyl groups. Genes can also be silenced by modification of the histone proteins that make up the "smart stuffing" of chromosomes. These chemical modifications are potentially epigenetic because they influence the expression of genes, but they are not part of the actual gene sequence.

When working properly, *ARID1A* codes for an important piece of an epigenetic regulatory molecule known as a chromatin-remodeling complex. Chromatin is the structure that a length of DNA makes with its support proteins. Chromatin remodeling changes that structure, suppressing or enabling the activity of genes.

In the past several years, other chromatin-modifying genes have been found to be mutated, for example in lung and kidney tumors, but these mutations are comparatively rare. The *ARID1A* mutations are the first such mutations to predominate within a given tumor type. "We call a gene that's involved in a major portion of cancers of a given type a 'mountain,'" says Vogelstein. "But in recent years, we've been finding fewer and fewer new mountains. That's one reason why this study is so exciting – *ARID1A* is a new one."

Vogelstein hopes the finding will stimulate further interest in the links between the genetics and epigenetics of cancer. Epigenetic changes have long been observed in cancer cells, but the reasons for these changes, such as how chromatin is remodeled, have been mysterious. "The *ARID1A* finding offers a

clue to the pathways that link cancer's genetics to its epigenetics," he says. "I suspect that mutations in chromatin-modifying genes such as *ARID1A* will now start to be found more often."

By tracing what happens at the molecular level inside cells after such genes are disrupted, scientists also might be able to develop new anti-cancer strategies. *ARID1A* appears to be a tumor suppressor gene, whose normal function serves as a brake on inappropriate cellular proliferation. Researchers generally find it hard to design drugs to replace lost "good" functions in tumor cells, and prefer to try to block "bad" functions that are inappropriately active. "If the disruption of *ARID1A* drives cancer by inappropriately activating some other pathway, then that pathway could, in principle, be targeted," says Vogelstein. "That's one of the issues that's going to be very important to address as we move forward."