Sequence of ovarian genome identifies predominant gene mutations, points to possible treatment

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The genome of the most common form of ovarian cancer is characterized by a few common gene mutations but also surprisingly frequent structural changes in the genome itself, said members of The Cancer Genome Atlas, including the Baylor College of Medicine Human Genome Sequencing Center, that sequenced and analyzed more than 300 such tumors. The study was the first to achieve an overview of this type of ovarian cancer.

"We found that ovarian cancer has a dramatic pattern of genomic disruption," said Dr. Richard Gibbs, director of the Baylor Human Genome Sequencing Center and an author of the report that appears in the current issue of the journal *Nature*. The BCM Center completed one-quarter of the sequencing.

Ovarian carcinoma (a form of cancer) is the fifth leading cause of cancer deaths among women in the United States. An estimated 21,880 cases and 13,850 deaths from the disease occurred in 2010. More than 70 percent of patients are not diagnosed until they have an advanced stage form of the disease, and the most common kind of ovarian cancer is serous ovarian adenocarcinoma– a high-grade form of which was sequenced by the researchers in this project. The National Cancer Institute and the National Human Genome Research Institute of the National Institutes of Health funded this project.

The researchers said in their report that the spectrum of gene mutations in the study "was surprisingly simple."

The study found that 96 percent of the tumors had mutated TP53 genes. When normal, this gene is a tumor suppressor. Its loss allows tumors to develop without check. Nine other mutated genes occur at much lower but statistically significant rates. Among these are NF1, BRCA1, BRCA2, RB1, and CDK12. BRCA1 and BRCA2 (known primarily as breast cancer genes) that were mutated in 30 percent of patients while the occurrence of the other mutations was much lower. Some BRCA1 and BRAC2 mutations were inherited while others occurred spontaneously in the breast tissue.

"A globally disrupted genome is the common theme in this cancer," said Gibbs. "Large-scale amplifications and deletions of chromosome segments make this cancer very complex."

"This landmark study is producing impressive insights into the biology of this type of cancer," said National Institutes of Health Director Dr. Francis Collins. "It will significantly empower the cancer research community to make additional discoveries that will help us treat women with this deadly disease. It also illustrates the power of what's to come from our investment in The Cancer Genome Atlas."

While the mutation pattern seemed simple, the researchers found that, this form of ovarian cancer "demonstrates a remarkable degree of genomic disarray."

In particular, the authors point to the frequency of somatic copy number variations, in which parts of the genome are duplicated or deleted in the tumors themselves. More than half of these tumors had defects in genes that play a role in the repair of defects that occur when cells divide and duplicate their DNA. The authors said that drugs called PARP inhibitors

are already used in this diseases and this explains why they are sometimes successful in treating the disease.

"We also defined a set of genes that were associated with worse or better patient outcome," said Dr. Chad Creighton, assistant professor in the division of biostatistics in the NCI-designated Dan L. Duncan Cancer Center at BCM. He and others on the Genome Atlas team identified a transcriptional signature of 193 genes that predicts survival. (The transcriptional signature involves assessing gene activity by measuring the types and quantities of RNA [genetic material that forms a template from which parts of cell make protein] cells produce.) They correlated 108 genes with poor survival and 85 genes with good survival.

While high-grade serous ovarian adenocarcinoma is conventionally considered as one type of cancer having uniform features, "we could divide the tumors into four different groups based on gene expression patterns," said Creighton. "They look like four different cancers."

"We were able to define a set of genes that were associated with worse outcomes versus better outcomes in patients," he said. They applied this gene signature to other sets of data collected about ovarian cancer and found that the profile predicted worse or better outcome there as well.

"These data are all public," said Creighton. "They are meant for people to use to find specific genes for research. They could influence a lot of future studies."

The Cancer Genome Atlas project was created to provide this kind of information for a host of cancers – some of which have already been sequenced and others underway or in the planning stages.

"This allows us to better characterize the disease at a molecular level and catalogue the genetic abberations," said Creighton. "This is a much more

comprehensive dataset than we have ever had before."

"The new knowledge of the genomic changes in ovarian cancer has revealed that the molecular catalysts of this disease are not limited to small changes affecting individual genes," said NCI Director Dr. Harold E. Varmus. "Also important are large structural changes that occur in these cancer genomes. Cancer researchers can use this comprehensive body of information to better understand the biology of ovarian cancer and improve the diagnosis and treatment of this dreaded disease."

More information: Spellman, et al. Integrated Genomic Analyses of Ovarian Carcinoma. *Nature*. June 30, 2011. DOI:10.1038/nature10166
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