Scientists identify unique genomic features in testicular cancer

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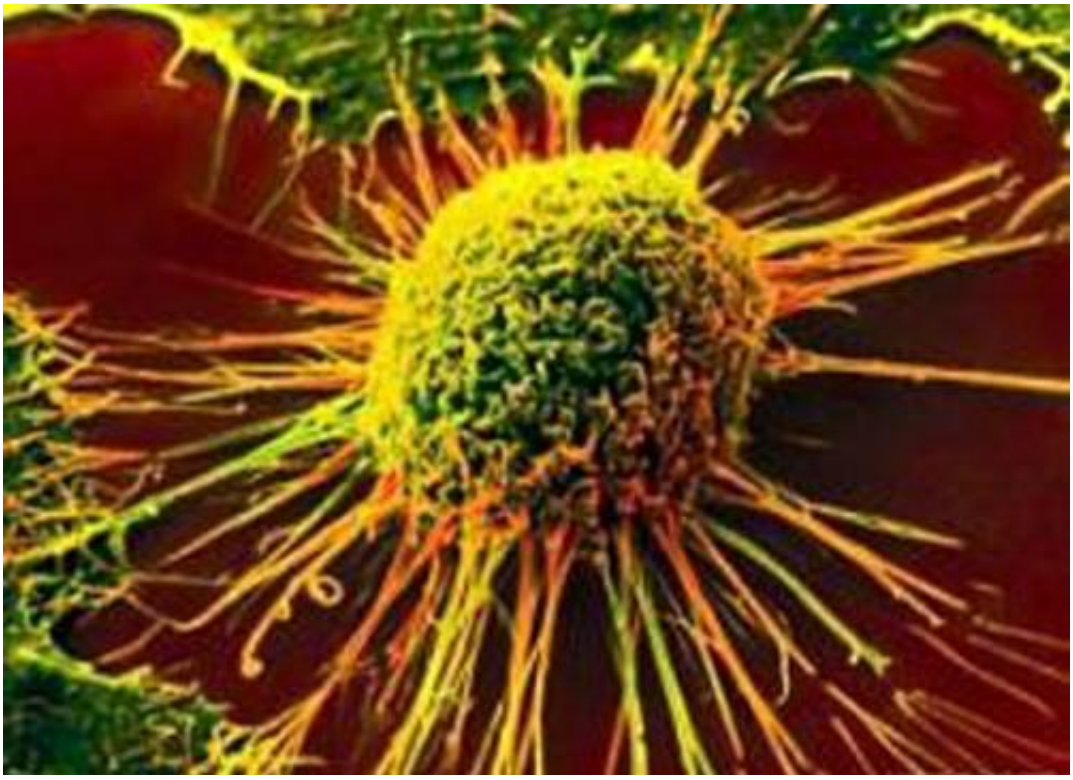

Researchers led by scientists at Dana-Farber Cancer Institute say they have identified unique genomic changes that may be integral to testicular cancer development and explain why the great majority are highly curable with chemotherapy - unlike most solid tumors.

The findings may shed light on factors in other cancers that influence their sensitivity to chemotherapy, according to a report in *Nature*.

Cancers of the testes are known as germ cell tumors (germ cells produce sperm and eggs). In 2016, about 8,720 new cases are expected in the U.S., with about 380 deaths. Although they are rare, primary testicular germ cell tumors are the most common solid cancers in young men.

Most of the tumors are highly sensitive to chemotherapy, and more than 80 percent of patients with germ cell tumors are cured, even when the cancer has metastasized. However, a significant number become chemotherapy-resistant, and about 10 percent of patients with metastatic germ cell tumors die as a result.

Previous studies of the genomes of testicular tumors revealed mutations and chromosome damage, but haven't pinpointed specific alterations or events linked to chemosensitivity or resistance.

The new research was carried out by scientists led by Eliezer Van Allen, MD, of Dana-Farber and the Broad Institute of MIT and Harvard, and Christopher Sweeney, MBBS, of Dana-Farber. In a comprehensive search for the critical genomic and molecular features of these cancers, the scientists analyzed samples of 59 tumors from 49 patients treated between 1997 and 2014 at Dana-Farber/Brigham and Women's Cancer Center (DF/BWCC) over a period.

The samples were studied with whole-exome DNA sequencing and RNA transcriptome analysis, and the findings were correlated with clinical outcomes data. Although mutated genes are the main drivers of many cancers, "we didn't find any one gene that really explains" the formation of testicular cancers, said Sweeney.

One feature of the tumors that had been previously reported was a gain

of extra DNA copies on one arm of chromosome 12, in a segment labeled 12p. Chromosomes carry two versions, or alleles, of DNA, one from each parent. In the new study, however, the scientists found there were many chromosome changes with multiple parts of the genome having gain of one parental allele while simultaneously losing a copy of the other parental allele - a type of chromosomal damage called reciprocal loss of heterozygosity (RLOH).

The gain and loss of DNA copies shows that the tumors' chromosomes "are profoundly deranged," said Van Allen, and represents "a hallmark feature we hadn't noticed before." This abnormality maybe linked to the development of germ cell tumors and cause them to be sensitive to chemotherapy, Van Allen said, but exactly how it does so remains to be discovered.

The analysis revealed another feature of the chemosensitive germ cell tumors - they possessed intact copies of the p53 gene. This gene directs cells to make a tumor-suppressor protein that clamps down on renegade cells so they can't form tumors. Many cancers contain mutated or lost p53 genes, indicating they have lost this protective factor.

Moreover, the researchers discovered that in contrast to most types of cancer, testicular tumor cells are already poised on the brink of self-destruction by apoptosis. Apoptosis, also known as programmed cell death, is the body's quality control process that gets rid of unneeded and dangerously abnormal cells. Many cancers have evolved strategies for blocking the cell's orders to self-destruct. The study results suggest that most testicular tumors may be highly susceptible to chemotherapy because their cells are already highly "primed" for apoptotic death, although why this is so hasn't been determined.

In another part of the study, the scientists studied 13 germ cell tumor samples taken from five patients over time, spanning from before they

underwent treatment to after the tumors became drug-resistant. As the cancers progressed, they showed increases in chromosomal abnormalities seen in all the tumors. The cells of the germ cell tumors also became more "differentiated" - a trait that's usually associated with less-aggressive cancers; this observation remains a puzzle, the authors said, but may explain the resistance of these tumors to chemotherapy.

Because of their rarity, germ cell tumors haven't been as intensively studied as other forms of cancer, and research funding is more scarce, Sweeney said. The new study, he said, "gives us insights into germ cell tumor biology that haven't been found to this degree and provide a strong base to explore these very interesting findings further."

More information: Genomic evolution and chemoresistance in germ-cell tumours, nature.com/articles/doi:10.1038/nature20596

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