Spotting DNA repair genes gone awry

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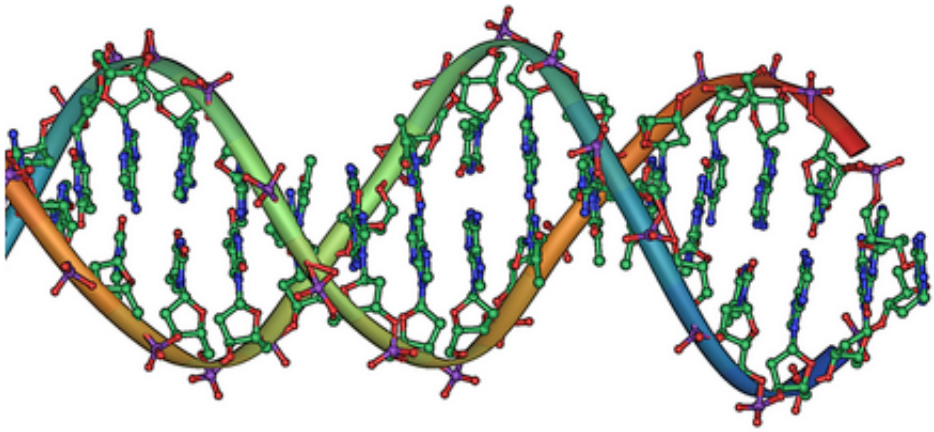

DNA double helix. Credit: public domain

Researchers led by Ludwig Cancer Research scientist Richard Kolodner have developed a new technique for sussing out the genes responsible for helping repair DNA damage that, if left unchecked, can lead to certain cancers.

Genome instability suppressing (GIS) genes play an important role in correcting DNA damage involving the improper copying or reshuffling of large sections of chromosomes. Called gross chromosomal rearrangements, or GCRs, these structural errors can disrupt gene order or even result in an abnormal number of chromosomes.

"Mutated GIS genes have long been suspected of playing a role in the development of many types of cancers, but identifying them has been difficult due in large part to a lack of comprehensive GCR tests, or assays, in mammalian systems," said Christopher Putnam, an associate investigator at the Ludwig Institute for Cancer Research, San Diego and one of the first authors of the study.

In the current issue of the journal *Nature Communications*, Putnam, Kolodner and their colleagues describe a novel two-pronged approach that combines methods from genetics and bioinformatics to identify GIS genes—first in yeast and then in humans.

"This is one of the first large-scale studies to integrate these two methods," said co-senior author Sandro de Souza, a professor of bioinformatics at the Federal University of Rio Grande do Norte's Brain Institute in Brazil, who received Ludwig support for this study.

In the first step, the scientists used assays and technologies developed by Kolodner—who is director of the Ludwig Institute for Cancer Research, San Diego and a distinguished professor of Cellular and Molecular Medicine at the University of California, San Diego, School of Medicine—and his lab to screen thousands of mutant yeast strains for genes that suppress GCRs. They identified 182 GIS genes, 98 of which had not been described before. "Ours is probably one of the most comprehensive lists of GIS genes in yeast to date," Putnam said.

The team also uncovered more than 400 previously unknown cooperating Genome Instability Suppressing genes (cGIS) genes, which only affect genome stability when combined with other mutations. "Before our experiment, only a few dozen cGIS genes were known. Now we know of hundreds," said Putnam, who is also an adjunct assistant professor of medicine at UC San Diego School of Medicine.

"These results have highlighted the complex genetic network that maintains genome integrity in normal cells," said first author Anjana Srivatsan, a postdoctoral fellow in Kolodner's lab at the Ludwig San Diego Branch and UC San Diego School of Medicine.

To determine how many of the yeast GIS genes had human counterparts implicated in cancers, the researchers searched The Cancer Genome Atlas (TCGA)—a compilation of genomic data from thousands of patients—for such human gene homologues.

They also supplemented their candidate list with human genes that are not found in yeast but that participate in the same pathways and protein complexes as the yeast GIS genes. "We didn't want to just look for the human equivalent of yeast GIS genes because there are human GIS genes that don't have yeast homologs," Putnam said.

Three cancers in the TCGA were selected for screening: ovarian cancer, colorectal cancer and acute myeloid leukemia. The scientists hypothesized that a greater number of GIS gene defects should be implicated in ovarian cancer and colorectal cancer because these two cancers tend to involve numerous large-scale rearrangements of the genome. Leukemia served as an important control because it is a cancer with little genome instability, and thus should not involve any GIS gene defects.

As expected, the team found that 93% of ovarian cancers and 66% of colorectal cancers had genetic defects affecting one or more of the predicted GIS genes, whereas acute myeloid leukemia did not appear to have defects involving GIS genes.

The researchers are already screening more than a dozen other human cancers in the TCGA for GIS gene defects. "Understanding this process allows us to think more about how carcinogenesis proceeds and it might

give us insights into defects that could be therapeutically actionable in the future," said Putnam.

More information: Christopher D. Putnam et al. A genetic network that suppresses genome rearrangements in Saccharomyces cerevisiae and contains defects in cancers, *Nature Communications* (2016). DOI: 10.1038/ncomms11256

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