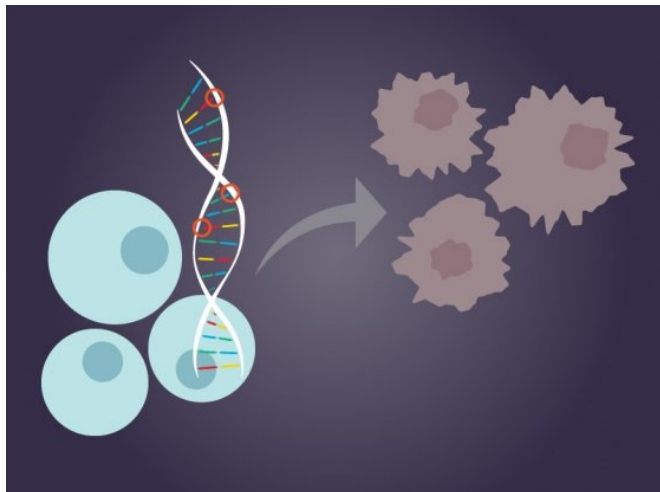


Add broken DNA repair to the list of inherited colorectal cancer risk factors

23 February 2018, by Tom Ulrich



Credit : Susanna M. Hamilton

An analysis of nearly 3,800 colorectal cancer patients—the largest germline risk study for this cancer to date—reveals opportunities for improved risk screening and, possibly, treatment.

Thirty percent of a given person's risk of colorectal [cancer](#) is hereditary. The genetic roots of that heritability, however, remain murky; the current list of colorectal cancer susceptibility genes only explains about 10 percent of the genetic risk.

To expose some of that "hidden" heritability, a multicenter team led by researchers at the Broad Institute of MIT and Harvard Cancer Program and Dana-Farber Cancer Institute screened nearly 3,800 colorectal cancer [patients](#) for inheritable (a.k.a. [germline](#)) [mutations](#) in 40 genes involved in DNA damage repair and not already linked to colorectal cancer risk.

Their results, reported in the *American Journal of Human Genetics*, reveal that a small but significant subset of patients do harbor inherited mutations in

DNA repair genes not previously linked to colorectal cancer risk.

Of the 680 patients the team initially screened, 31 carried inherited disease-promoting mutations in known colorectal cancer risk genes such as APC or TP53. Unexpectedly, an additional 33 carried at least one germline mutation in 21 of the 40 DNA repair genes examined. Three and five, respectively, of those patients carried mutations in ATM or PALB2, two elements of a DNA repair process called homologous recombination (HR). Previous studies have linked inherited mutations affecting HR to breast, pancreatic, and prostate cancer risk, but not colorectal cancer. Together, the inherited ATM and PALB2 mutations helped explain increased disease risk in an additional 20 percent of colorectal cancer patients than the current list of risk genes.

Also noteworthy, the team found no difference in age at diagnosis or family history between germline mutation-carrying and non-carrying patients. At the moment age and family history are two key factors doctors consider when deciding whether to screen colorectal cancer patients for germline risk mutations.

The team validated their results from the first 680 patients in another 3,117—making this the largest germline risk mutation study in colorectal cancer to date.

Taken together, the team's findings suggest four things:

1. Inherited ATM and PALB2 mutations should be added to the list of colorectal cancer risk [genes](#) and to standard tumor genetic testing panels.
2. Breast and prostate tumors with germline HR defects often respond to a class of drugs called PARP inhibitors. Colorectal cancer patients whose tumors harbor

similar mutations may also benefit from these treatments.

3. According to the Exome Aggregation Consortium browser, between 1 in 400 and 1 in 1000 people of European ancestry carry germline ATM or PALB2 mutations, opening opportunities for improved risk and prevention screening.
4. It may be that germline risk mutation screening should be standard for all [colorectal cancer](#) patients, regardless of age or family history.

More information: Saud H. AlDubayan et al. Inherited DNA-Repair Defects in Colorectal Cancer, *The American Journal of Human Genetics* (2018). [DOI: 10.1016/j.ajhg.2018.01.018](https://doi.org/10.1016/j.ajhg.2018.01.018)

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