

## **NIEHS scientists find proteins involved in immunity potentially cause cancer**

By Robin Arnette

A set of proteins involved in the body's natural defenses produces a large number of mutations in human DNA, according to a new [study](http://www.nature.com/ng/journal/vaop/ncurrent/abs/ng.2702.html) (<http://www.nature.com/ng/journal/vaop/ncurrent/abs/ng.2702.html>) led by researchers at NIEHS. The findings suggest that these naturally produced mutations are just as powerful as known cancer-causing agents in producing tumors.

The proteins are part of a group called apolipoprotein B mRNA-editing enzyme catalytic polypeptide-like (APOBEC) cytidine deaminases. The investigators found that APOBEC mutations can outnumber all other mutations in some cancers, accounting for over two-thirds in some bladder, cervical, breast, head and neck, and lung tumors.

The scientists published their findings online July 14 in the journal *Nature Genetics*. [Dmitry Gordenin, Ph.D.](#), is corresponding author of the paper and a senior associate scientist at NIEHS. He said researchers knew the main functions of APOBEC cytidine deaminases were to inactivate viruses that attack the body, and prevent ancient viruses present in the human genome from moving around and causing disrupting mutations. Because they are so important to normal physiology, he and his collaborators were surprised to find a dark side to them - that of mutating human chromosomal DNA.

### **Linking mutations across the genome to the environment**

The study is a follow-up to one Gordenin and his group [published](http://www.ncbi.nlm.nih.gov/pubmed/22607975) (<http://www.ncbi.nlm.nih.gov/pubmed/22607975>)

in *Molecular Cell* in 2012, after they discovered APOBECs could generate clusters of mutations in some cancers.

"The presence of APOBEC clusters in the genome of tumor cells indicates that APOBEC enzymes could also have caused many mutations across the genome," Gordenin said.

Gordenin's NIEHS team, comprised of scientists from the Chromosome Stability Group, headed by Michael Resnick, Ph.D., and the Integrative Bioinformatics Group, headed by David Fargo, Ph.D., took the 2012 research one step further, by applying a modern data science approach.

The group collaborated with co-corresponding author Gad Getz, Ph.D., and other colleagues from the Broad Institute of MIT and Harvard in Cambridge, Mass. They looked for signs of genome-wide APOBEC mutagenesis in cancers listed in The Cancer Genome Atlas, a cancer database funded and managed by the National Cancer Institute and the National Human Genome Research Institute, both part of the National Institutes of Health.

Using APOBEC's distinctive DNA mutational signature, they examined approximately 1 million mutations in 2,680 cancer samples, and found that, in some tumors, nearly 70 percent of mutations in a given specimen resulted from APOBEC mutagenesis. The mutation pattern, which appeared in clusters and individual mutations, could affect many cancer-associated genes.

Steven Roberts, Ph.D., a postdoctoral fellow who works with Gordenin, is first author on both studies. He explained that since APOBECs are regulated by the immune system, which is responsive to many environmental factors, he believes there may be a significant environmental component to APOBEC mutagenesis.

Listen to Roberts describe the duality of APOBEC  
(00:29)

[Listen Now](#) (230KB)

[Transcript](#) (12KB)

"We hope that determining the environmental link to these mutations will lead to viable cancer prevention strategies," Roberts said.



*Gordenin, left, and Roberts said the environmental aspect of APOBEC mutagenesis is directly related the Institute's mission, and an area they are currently investigating. (Photo courtesy of Steve McCaw)*

In upcoming work, he and Gordenin plan to address why APOBEC mutagenesis appears in some cancer types and not others.

Listen as Gordenin discusses the advances made possible through data science (00.46)

[Listen Now](#) (370KB)

[Transcript](#) (12KB)

*Citation:* Roberts SA, Lawrence MS, Klimczak LJ, Grimm SA, Fargo D, Stojanov P, Kiezun A, Kryukov GV, Carter SL, Saksena G, Harris S, Shah RR, Resnick MA, Getz G, Gordenin DA.

(<http://www.nature.com/ng/journal/vaop/ncurrent/abs/ng.2702.html>)

2013. An APOBEC cytidine deaminase mutagenesis pattern is widespread in human cancers. Nat Genet; doi:10.1038/ng.2702 [Online 14 July 2013].

---

The Environmental Factor is produced monthly by the [National Institute of Environmental Health Sciences \(NIEHS\)](#)

(<http://www.niehs.nih.gov/>)

, Office of Communications and Public Liaison. The content is not copyrighted, and it can be reprinted without permission. If you use parts of Environmental Factor in your publication, we ask that you provide us with a copy for our records. We welcome your [comments and suggestions](#). ([bruskec@niehs.nih.gov](mailto:bruskec@niehs.nih.gov))

This page URL: NIEHS website: <http://www.niehs.nih.gov/>

Email the Web Manager at [webmanager@niehs.nih.gov](mailto:webmanager@niehs.nih.gov)