

# Mutations in Noncoding Regions of Human Genome Also Cause Cancer, Study Shows

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While the best described cancer mutations are in regions that provide instructions to make proteins, most mutations actually happen in the noncoding regions of our genome, researchers found.

University of California researchers identified 200 new mutations in noncoding DNA that drive tumor formation and growth. Their findings may lead to new, personalized therapies for cancer, including [multiple myeloma](#).

The study, "[A global transcriptional network connecting noncoding mutations to changes in tumor gene expression](#)," was published in the journal *Nature Genetics*.

Roughly 98 percent of the human genome is composed of what scientists used to call "junk" DNA because it did not code for any genes. However, with the advance in genomics, scientists found that these portions of DNA play a key role in regulating how cells work.

Given that most of our genome is composed of noncoding DNA, it is not surprising that most cancer-driving mutations are in those regions. But how they influence tumor development is still unclear.

"Interpretation of noncoding mutations poses particular challenges owing to the very large number of events and a limited understanding of their functional consequences," researchers wrote.

Researchers have been trying to study these mutations for a while, but studies to date have

only identified one single noncoding mutation linked to cancer. This mutation is located in the promoter of the *TERT* gene, increasing its expression and helping cells become immortal.

Now, researchers at the University of California San Diego Cancer School of Medicine and Moore's Cancer Center used a different strategy. They analyzed the entire genome of 930 human tumors and examined gene expression profiles in these samples to understand how mutations in these noncoding regions influence gene expression.

“The secret sauce was to look for changes in gene expression,” Trey Ideker, PhD, a professor at UC San Diego School of Medicine and Moore's Cancer Center, said in a press release.

Their analysis identified nearly 200 mutations in noncoding regions that had an impact in gene expression, and went on to test three of those mutations in further experiments.

“Most cancer-related mutations occur in regions of the genome outside of genes, but there are so incredibly many of them that it's hard to know which are actually relevant and which are merely noise,” said Ideker, the study's senior author.

“Here for the first time we found about 200 mutations in noncoding DNA that are functional in cancer — and that's about 199 more than we knew before,” he said.

The “three examples we tested experimentally do support a causal link from mutation to expression changes,” researchers wrote.

“One example that stood out was a noncoding mutation affecting a gene called DAAM1,” said Wei Zhang, PhD, the study's first author. “DAAM1 activation makes tumor cells more aggressive, and better able to invade surrounding tissues.”

Besides DAAM1, they found that two other noncoding mutations affected one gene called *MTG2*, important to keep the cell's energy factories working properly, and one gene called *HYI*, important for the metabolism of cells.

Researchers will now investigate how noncoding and coding mutations are linked in cancer, and try to identify mutational patterns with prognostic value.