

# CRISPR-Based Tool Maps Gene Function in Human Cells

The researchers hope to soon increase the scale of their gene mapping to focus on diseases such as lung cancer and prostate cancer.

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UC San Francisco scientists have used a high-throughput CRISPR-based technique to rapidly map the functions of nearly 500 genes in human cells, many of them never before studied in detail.

The research generated a vast amount of novel genetic data, including identifying new genes involved in cellular energy production and explaining a long-standing mystery about why some cholesterol drugs can be used to treat osteoporosis while related drugs have no such effect. But the most important takeaway, the researchers say, is the novel framework the study demonstrates for comprehensively mapping the function of genes within human cells, which they hope to eventually extend to the whole human genome.

“We have a good understanding of the functions of about 1,000 to 2,000 critical human genes that — deservedly — have been very well studied,” said UCSF cancer biologist [Luke Gilbert](#), PhD, one of the new study’s two senior authors. “But that’s less than 10 percent of the 25,000 genes in the human genome. Of the rest, perhaps half have been studied at least a little by someone, and the other half we know next to nothing about.”

“This is not surprising, because the experiments needed to test gene function are expensive and time consuming, so you need to prioritize the genes you think are probably the most important,” added Max Horlbeck, PhD, who recently completed his doctoral work in the lab of UCSF cell biologist [Jonathan Weissman](#), PhD, the study’s second senior author. “But there are mysteries hiding in the rest of the genome that could lead to brand new treatments for a wide variety of diseases, and now we have a technique that can quickly and comprehensively map out how these unstudied genes fit into our broader understanding of biology.”

In their new study, published July 19, 2018, in [Cell](#), Horlbeck and colleagues used a technique called genetic interaction mapping, which has been perfected in the past decade to build comprehensive understanding of gene functions in yeast, but had never before been successfully applied at a large scale to human cells.

The approach involves systematically shutting down pairs of genes in individual cells and

measuring how the cells respond, which teaches researchers about the relationship between the two genes. In some cases, scientists observe that shutting down either gene in a pair does as much damage to the cell as shutting down both, which suggests that the two genes are part of the same functional system — much as removing two different components of a car’s steering system would have a similar effect on the car’s ability to turn. This kind of data lets researchers quickly identify genes of unknown function as parts of larger functional systems.

In contrast, researchers can also identify pairs of genes that have independent but synergistic functions, when shutting down both genes has a dramatically larger effect on cells than shutting down either gene on its own. If your car’s main brakes aren’t working, the problem is much worse if your emergency brake is out, too. The strategy of targeting such synergistic relationships — known as synthetic lethality — is a major priority of drug companies seeking to target diseases such as prostate cancer because it allows them to design powerful combination therapies that target multiple cellular pathways at once to gain a more dramatic effect.

### Genetic Links to Energy Metabolism, DNA Repair and Osteoporosis

In the new study, Horlbeck and colleagues performed interaction mapping on 472 genes that previous experiments had linked to cellular growth and survival. To do this, they used a tool called [CRISPR inhibition](#) (CRISPRi), a version of the CRISPR gene-editing system that turns down the volume on a gene’s activity without editing the DNA itself, which was [developed for use in mammalian cells by the Weissman lab](#) in 2013 (also see the lab’s [2016 study](#) decoding the functions of non-coding RNA molecules).

Here the researchers used CRISPRi to systematically inactivate pairs of genes in two different leukemia cell lines — one representing acute lymphoblastic leukemia and the other chronic myeloid leukemia — while measuring the effect on cell growth. The resulting map of 111,628 unique two-gene interactions allowed the researchers to cluster the 472 genes according to their relationships with one another, and to assign these clusters functional meanings, such as specific biological pathways or locations within the cell.

“While our previous work establishing the CRISPRi screening technology allowed us to simply identify which genes are important in a given context, such as cancer cell proliferation, this extends that to allow us to ask what is the function of each gene that makes it so important,” Weissman said.

The researchers showed that their new gene interaction maps captured 80 percent of known functional relationships between the genes being studied, but that the majority of strong interactions revealed by the new data were novel — not catalogued in standard databases of gene function. These included many gene pairs which were not known to interact directly but had been independently associated with the formation of protein complexes or with cellular processes such as energy production. Other novel gene interactions revealed genes involved in protein synthesis and DNA repair, two other key cellular functions that play a role in numerous diseases.

### Cellular Pathways Regulating Cholesterol Metabolism, DNA Damage Repair

Among other findings, the researchers were surprised to note significant differences in mitochondrial energy production pathways between the two subtypes of leukemia they studied. “You would expect such essential gene pathways to be hard-wired — the same in skin cells or leukemia cells,” Gilbert said. “But discovering differences between these two cell lines suggests that you could come up with distinct ways to target energy production in these cancers therapeutically. That’s particularly exciting for T-cell acute lymphoblastic leukemia, which doesn’t have a lot of great targeted drugs.”

Finally, the researchers discovered a novel synthetic lethal relationship between cellular pathways regulating cholesterol metabolism and those regulating DNA damage repair. Specifically, the researchers noticed that when they inactivated a gene called FDPS, which is involved in producing cholesterol, cells became highly dependent on a DNA repair gene called HUS1 for their survival.

“Right away it didn’t make a whole lot of sense why interfering with cholesterol synthesis would make cells dependent on the DNA damage response,” Horlbeck said. “It made even less sense when we looked at another gene just a few steps away in the cholesterol synthesis pathway and found that it had no interaction with DNA repair genes at all.”

Further experiments suggested a possible solution to this puzzle — one that might also solve a long-standing pharmacological mystery. The FDPS gene is responsible for modifying a chemical called IPP on its way to producing cholesterol. When FDPS is suppressed, IPP builds up in the cell and — the researchers believe — causes damage to DNA that requires constant repair for the cell to survive.

Importantly, FDPS is the target of a class of anti-cholesterol drugs called bisphosphonates, which have the useful side effect of increasing bone density. This has made them one of the leading treatments for osteoporosis, which affects approximately 30 percent of postmenopausal women in the U.S. Why an anti-cholesterol drug should affect bone density has never been clear, and drug companies have tried and failed to produce similar therapeutic effects with other cholesterol drugs such as the blockbuster Lipitor.

The new data suggest why: bisphosphonates, but not other anti-cholesterol drugs, may trigger DNA damage via buildup of IPP in osteoclasts, the bone-destroying cells implicated in osteoporosis. By reducing the number of osteoclasts, the drug could help restore bone density in a way other anti-cholesterol drugs would not.

The researchers hope to soon increase the scale of their gene mapping experiments in human cells to focus on additional diseases such as lung cancer and prostate cancer and to focus on identifying genes responsible for drug response and drug resistance.

“Up until now science has produced a lot of data about specific mutations that drive human diseases, and we have a pretty good idea about which cells express what genes across human body, but we fundamentally don’t understand how genes work together in human cells,” Gilbert said. “With this new approach we are starting to build a portrait of how genetic interactions keep tissues healthy or to drive disease processes, but there is a whole lot more to learn.”

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