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Screen of human genome reveals set of genes essential for cellular viability

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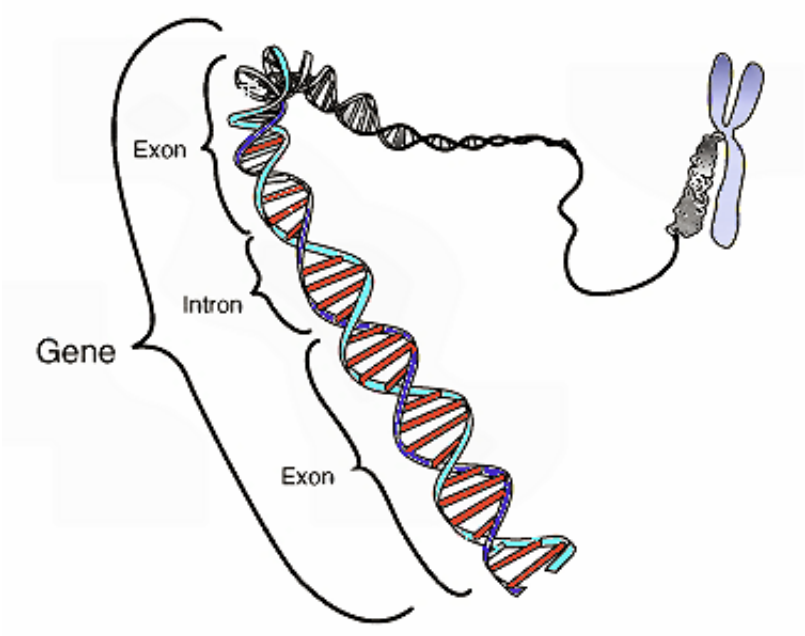

This image shows the coding region in a segment of eukaryotic DNA. Credit: National Human Genome Research Institute

Using two complementary analytical approaches, scientists at Whitehead Institute and Broad Institute of MIT and Harvard have for the first time identified the universe of genes in the human genome essential for the survival and proliferation of human cell lines or cultured human cells.

Their findings and the materials they developed in conducting the research will not only serve as invaluable resources for the global

research community but should also have application in the discovery of drug-targetable genetic vulnerabilities in a variety of human cancers.

Scientists have long known the essential genes in microorganisms, such as yeast, whose genomes are smaller and more easily manipulated. Most common yeast strains, for example, are haploid, meaning that genes exist in single copies, making it fairly simple for researchers to eliminate or "knock out" individual genes and assess the impact on the organism. However, owing to their greater complexity, diploid mammalian genomes, including the human genome, have been resistant to such knockout techniques—including RNA interference, which is hampered by off-target effects and incomplete gene silencing.

Now, however, through use of the breakthrough CRISPR (for clustered regularly interspersed short palindromic repeats) genome editing system, researchers in the labs of Whitehead Member David Sabatini and Broad Institute Director Eric Lander have been able to generate a genome-wide library of single-guide RNAs (sgRNAs) to screen for and identify the genes required for cellular viability. The sgRNA library targeted slightly more than 18,000 genes, of which approximately 10% proved to be essential. These findings are reported online this week in the journal *Science*.

"This is the first report of human cell-essential genes," says Tim Wang, a graduate student in the Sabatini and Lander labs and first author of the *Science* paper. "This answers a question people have been asking for quite a long time."

As might have been expected, Wang says that many of the essential genes are involved in fundamental biological processes, including DNA replication, RNA transcription, and translation of messenger RNA. But, as Wang also notes, approximately 300 of these essential genes are of a class not previously characterized, are largely located in the cellular

compartment known as the nucleolus, and are associated with RNA processing. Wang says the precise function of these genes is the subject of future investigation.

To validate the results of the CRISPR screens, the group took the added step of screening for essential genes in a unique line of haploid human cells. Using an approach known as gene-trap mutagenesis (a method pioneered in part by former Whitehead Fellow Thijn Brummelkamp) in the haploid cells and comparing it to the CRISPR results, the researchers found significant, consistent overlap in the gene sets found to be essential. In a final step, the group tested their approaches in cell lines derived from two cancers, chronic myelogenous leukemia (CML) and Burkitt's lymphoma, both of which have been extensively studied. The novel method not only identified the essentiality of the known genes—in the case of CML, it hit on the BCR and ABL1 genes, whose translocation is the target of the successful drug Gleevec—but also highlighted additional genes that may be therapeutic targets in these cancers.

"The ability to zero in on the essential genes in the highly complex human system will give us new insight into how diseases, such as cancer, continue to resist efforts to defeat them," Lander says.

Wang, Lander, and Sabatini are enthusiastic about the potential applications of their work, as it should accelerate the identification of cancer drug targets while enhancing our understanding of the evolution of drug resistance, a major contributor to therapeutic failure. The researchers attribute this vast potential to the rigor that CRISPR brings to human genetics.

"This is really the first time we can reliably, accurately, and systematically study genetics in mammalian cells," Sabatini says. "It's remarkable how well it's working."

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David Sabatini's primary affiliation is with Whitehead Institute for Biomedical Research, where his laboratory is located and all his research is conducted. He is also a Howard Hughes Medical Institute investigator and a professor of biology at Massachusetts Institute of Technology.

More information: "Identification and characterization of essential genes in the human genome" *Science*, www.sciencemag.org/lookup/doi/… 1126/science.aac7041

Provided by Whitehead Institute for Biomedical Research