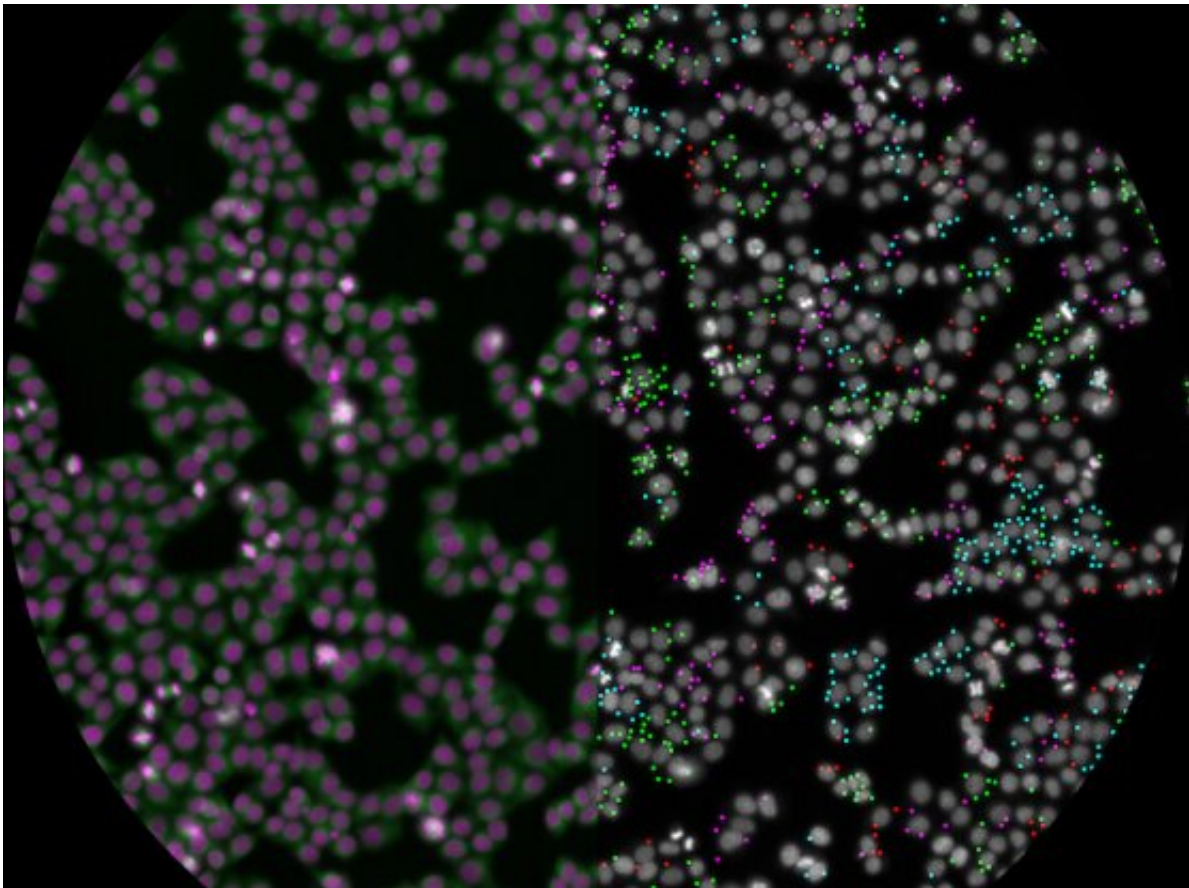


Scientists unveil the functional landscape of essential genes

November 8 2022, by Nicole Davis



Each cell in a pool was sequenced in place to identify which gene was disrupted (right half of the image), and measured microscopically to determine the disruption's functional consequences (left half). Credit: Luke Funk

A team of scientists at Whitehead Institute and the Broad Institute of

MIT and Harvard have systematically evaluated the functions of more than 5,000 essential human genes using a novel, pooled, imaged-based screening method. Their analysis harnesses CRISPR/Cas9 to knock out gene activity and forms a first-of-its-kind resource for understanding and visualizing gene function in a wide range of cellular processes with both spatial and temporal resolution.

The team's findings, published in the journal *Cell*, span over 31 million [individual cells](#) and include [quantitative data](#) on hundreds of different parameters that enable predictions about how genes work and operate together.

"For my entire career, I've wanted to see what happens in cells when the function of an essential gene is eliminated," said Iain Cheeseman, a senior author of the study and a member of Whitehead Institute. "Now, we can do that, not just for one gene but for every [single gene](#) that matters for a human cell dividing in a dish, and it's enormously powerful. The resource we've created will benefit not just our own lab but labs around the world."

Essential genes control basic functions that the cell requires in order to survive (transcription, mRNA splicing, translation, vesicle trafficking, DNA replication, cell division, etc.). Systematically disrupting the function of such genes is not a new concept, but conventional methods have been limited by various factors, including cost, feasibility, and the ability to fully eliminate the activity of essential genes.

Cheeseman, who is also the Herman and Margaret Sokol Professor of Biology at the Massachusetts Institute of Technology (MIT), and his colleagues collaborated with Paul Blainey and his team at Broad to define and realize this ambitious joint goal. The Broad researchers have pioneered a new genetic screening technology that marries two approaches—large-scale, pooled, [genetic screens](#) using CRISPR/Cas9

and imaging of cells to reveal both quantitative and qualitative differences. Moreover, the method is inexpensive compared to other methods and is practiced using commercially available equipment.

"We are proud to show the incredible resolution of cellular processes that are accessible with low-cost imaging assays in partnership with Iain's lab at the Whitehead Institute," said Blainey, a senior author of the study, a core institute member at Broad, associate professor of biological engineering at MIT, and member of the Koch Institute for Integrative Cancer Research at MIT.

"And it's clear that this is just the tip of the iceberg for our approach. The ability to relate genetic perturbations based on even more detailed phenotypic readouts is imperative, and now accessible, for many areas of research going forward."

Cheeseman added, "The ability to do pooled cell biological screening just fundamentally changes the game. You have two cells sitting next to each other and so your ability to make statistically significant calculations about whether they are the same or not is just so much higher, and you can discern very small differences."

Cheeseman, Blainey, lead authors Luke Funk and Kuan-Chung Su, and their colleagues evaluated the functions of 5,072 essential genes in a human cell line. They analyzed four markers across the cells in their screen—DNA; the DNA damage response, a key cellular pathway that detects and responds to damaged DNA; and two important structural proteins, actin and tubulin.

In addition to their primary screen, the scientists also conducted a smaller, follow-up screen focused on some 200 genes involved in cell division (also called "mitosis"). The genes were identified in their initial screen as playing a clear role in mitosis but had not been previously

associated with the process. These data, which are made available via a companion website called Vesuvius, provide a resource for other scientists to investigate the functions of genes they are interested in.

"There's a huge amount of information that we collected on these cells. For example, for the cells' nucleus, it is not just how brightly stained it is, but how large is it, how round is it, are the edges smooth or bumpy?" said Cheeseman. "A computer really can extract a wealth of spatial information."

Flowing from this rich, multi-dimensional data, the scientists' work provides a kind of cell biological "fingerprint" for each gene analyzed in the screen. Using sophisticated computational clustering strategies, the researchers can compare these fingerprints to each other and construct potential regulatory relationships among genes. Because the team's data confirms multiple relationships that are already known, it can be used to confidently make predictions about genes whose functions and/or interactions with other genes are unknown.

There are a multitude of notable discoveries to emerge from the researchers' screening data, including a surprising one related to ion channels. Two genes, AQP7 and ATP1A1, were identified for their roles in mitosis, specifically the proper segregation of chromosomes. These genes encode membrane-bound proteins that transport ions into and out of the cell. "In all the years I've been working on mitosis, I never imagined [ion channels](#) were involved," said Cheeseman.

He added, "We're really just scratching the surface of what can be unearthed from our data. We hope many others will not only benefit from—but also build upon—this resource."

More information: Luke Funk et al, The phenotypic landscape of essential human genes, *Cell* (2022). [DOI: 10.1016/j.cell.2022.10.017](https://doi.org/10.1016/j.cell.2022.10.017)

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