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CANCER CELLS ARE known for the rampant disorder in their genomes: extra or absent chromosomes or parts of chromosomes, long stretches of DNA gone missing or present in too many copies. “It looks like someone threw a stick of dynamite into the nucleus,” says HHMI Investigator Stephen Elledge of Harvard Medical School and Brigham and Women’s Hospital. “It’s a real mess.”

This chaotic state is called aneuploidy. It stems from errors during cell division causing the daughter cells to have abnormal numbers of chromosomes or chromosome fragments. Aneuploidy affects hundreds or thousands of genes and can wreak all kinds of havoc, including miscarriages, lethal birth defects, and disorders like Down syndrome.

Whether aneuploidy foments cancer is a 100-year-old mystery that scientists have largely neglected, according to Elledge. They’ve focused instead on potent single-gene mutations called “cancer drivers.” Some of these drivers disable tumor suppressor genes, allowing unruly cell division. Others send growth-promoting oncogenes into overdrive.

But Elledge suspected aneuploidy was an important part of the story. Based on his group’s latest research, Elledge says these massive alterations have evolved because they give malignant cells an edge in the “brutal competition” to win out over normal cells.

Their research is described in a paper in Cell in November 2013 that built on the group’s July 2012 report in Science.

His team devised computational methods to analyze mutation patterns in 8,200 tumors containing more than one million mutations. From these results they identified a large number of tumor suppressors (also known as STOP genes) of varying potency. The more potent a tumor suppressor, the greater its potential for causing cancerous growth if disabled by a mutation. They also identified a list of oncogenes along a continuum of strength, based on their pro-growth effect if mutated. The researchers estimated the genes’ potency by the frequency with which they were lost or gained in the cancer cells’ evolution.

Elledge then predicted that chromosomes on which the cumulative impact of STOP genes outweighed that of GO genes (the oncogenes and “essential genes” needed for normal or cancerous growth) would be more frequently deleted in cancer cells—in effect, disabling the normal brakes on cell growth. He tested this hypothesis using statistical methods and found the predictions were accurate to a degree that surprised even him. He also found the converse to be true, that chromosomes on which the cumulative impact of GO genes outweighed that of STOP genes were often amplified.

“Knowing the identity and likely potency of these cancer drivers has allowed us to uncover a driving force behind the selection of losses and gains of chromosome arms or whole chromosomes,” notes Elledge. “We have basically answered the question: Does aneuploidy drive cancer? We believe it does.”

Wiping Out Entire Clusters
Because chromosomes exist in pairs, the loss of single chromosomes affects only one copy of a given gene. The second copy on the partner chromosome remains intact. As a result, these “hemizygous” losses have a weaker effect on cancer growth than the mutation of both copies of a tumor suppressor gene. But the additive combination of groups of hemizygous losses can have a large impact.

In addition to aneuploidy, there are also recurring deletions of specific segments of chromosomes. “It turns out there are more STOP genes in these focal deletions than you would expect to occur randomly,” Elledge says. “So that brought up the idea that maybe a cancer cell is looking for these clusters of tumor suppressors, and wiping out an entire

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cluster at once—getting a bigger punch, a bigger bang for their buck.”

To those familiar with the “two-hit” model of cancer, it may come as a surprise that loss of a single gene copy can have an effect. According to this model, a mutation in a single copy of a tumor suppressor gene does nothing because the second copy compensates, and only if that second copy is subsequently “hit,” or mutated, does the cell begin its malignant journey.

However, Elledge cites evidence that a large proportion of cancer-suppressing genes are “haploinsufficient”—loss of even one copy can contribute to cancer development. In fact, Elledge estimates that 30 percent of all genes in humans are haploinsufficient, which has important implications for human development and disease.

“Losing or gaining single copies of genes on their own may have small effects, but altering many at the same time gives the cancer cell an advantage,” says Angelika Amon, a biologist and HHMI investigator at the Massachusetts Institute of Technology who studies aneuploidy. “Once you see [Elledge’s findings], you realize these losses and gains are not random noise in tumors, and we can begin to understand them.” —Richard Saltus