Scientists map all mammalian gene interactions

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This map of subnetwork centered around the gene cyclooxygenase-1 (COX1 or PTGS1) involved in synthesis of prostaglandins, which control smooth muscle activity in the body along with many other physiological functions. Credit: UCLA

In one of the first efforts of its kind, UCLA researchers have taken mammalian genome maps, including human maps, one step further by showing not just the order in which genes fall in the genome but which

genes actually interact.

The findings, published in the August issue of the journal *Genome Research,* will help researchers better understand which genes work together and shed light on how they collaborate to help cells thrive or die.

Mammals, including humans, have roughly 20,000 different genes. Genes hold instructions to create proteins that determine not only physical characteristics, like outward appearance, but all bodily processes, from moving blood through the veins to stimulating the immune system to attack a cold virus. They can also be pivotal in the development of diseases like cancer.

Each mammalian cell contains the full complement of genes, although depending on the activity of the cell, not all the genes are active. The genes engage not only in one-on-one interactions but also create wide networks involving dozens of genes. Little had previously been known about which genes work together most often in mammals and the networks they form.

For this study, the UCLA scientists used human radiation hybrid genome maps developed several years ago for the worldwide Human Genome Project, as well as several other mammalian radiation hybrid maps, for dogs, cats and mice.

They found substantial overlap and commonalities between gene interactions and networks across all four species, thus creating the first complete and comprehensive genetic interaction maps for mammalian cells.

Previous research had mapped interactions between proteins, which are set in motion by genes, but not the genes themselves, which provide

more direct and nearly comprehensive
information about the connection strength between genes. Researchers say this is an important step in furthering the understanding of the role each gene plays in triggering a process or function in the body.

"We were surprised that no one had done this before and that it worked so well," said study author Desmond Smith, a professor of molecular and medical pharmacology at the David Geffen School of Medicine at UCLA. "Modern genome science, although still in its infancy, has accumulated enormous amounts of information that can be repurposed to produce findings such as ours for decades to come. We've just scratched the surface."

To explore the gene interactions, the scientists statistically tested how often one gene appeared with another gene in a cell and which ones appeared together most often.

They determined that genes that frequently appear simultaneously in the radiation hybrid cells, even though they reside far apart on the genome, must be coming together for biological interactions. They found a network of more than 7 million interactions encompassing essentially every one of the genes in the mammalian genome.

The new findings go beyond just understanding where a gene is located, based on DNA sequencing — that is, the order in which they reside in a cell.

"Current genetic maps show the order of genes and where they physically reside, like a street map of homes," Smith said. "We took it one step further and were able to map which genes interact when they leave their homes and go to work."

"By looking at a gene's network of 'friends and co-workers,' we can tell a

lot about its role and purpose," said study author Andy Lin, a postdoctoral researcher in the UCLA Department of Molecular and Medical Pharmacology. "Mapping gene interactions is useful for both basic science and clinical research."

According to the researchers, some genes were found to have more extensive interactions than others, which may be helpful in finding specific drug targets to fight diseases such as cancer.

Smith compared the gene networks involved in promoting disease to the criminal world.

"The most well-connected gene represents someone powerful, like Al Capone, surrounded by his gang of mobsters. If we don't have a drug to target this main gene, there may be an existing drug that will effectively knock out a second-in-command, launching a flank attack that would cripple the primary gene's actions."

The findings, the researchers said, will help researchers in the field.

"The UCLA interaction map is a significant one that will help broaden the understanding of the working relationships between genes," said Tara C. Matise, an associate professor in the department of genetics at Rutgers University and director of the Laboratory of Computational Genetics, who was not part of the study. "The more information we acquire about genetic interactions, the more effective scientists can be in developing bench-to-bedside research."

Now that the researchers have mapped these interactions, the next step is to conduct biological experiments to further understand these interactions and how the genes work together.

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