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In a genetic research first, researchers turn zebrafish genes off and on

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Mayo Clinic researchers have designed a new tool for identifying protein function from genetic code. A team led by Stephen Ekker, Ph.D., succeeded in switching individual genes off and on in zebrafish, then observing embryonic and juvenile development. The study appears in the journal *Nature Methods*.

The work could help shed light on health-related problems such as how cancerous cells spread, what makes some people more prone to heart attacks, or how genes factor in addiction. More complicated issues, like the genetics of behavior, plasticity and cellular memory, stress, learning and epigenetics, could also be studied with this method.

The research at Mayo Clinic's Zebrafish Core Facility could help further unify biology and genomics by describing the complex interrelations of DNA, gene function and gene-protein expression and migration. The study examines protein expression and function from 350 loci among the zebrafish's approximately 25,000 protein-encoding genes. Researchers plan to identify another 2,000 loci.

"I consider this particular system a toolbox for answering fundamental scientific questions," says Dr. Ekker, a Mayo Clinic molecular biologist and lead author of the article. "This opens up the door to a segment of biology that has been impossible or impractical with existing genomics research methods."

For the First Time

The study includes several technical firsts in genetic research. Those include a highly effective and reversible insertional transposon mutagen. In nearly all loci tested, endogenous expression knockdown topped 99 percent.

The research yielded the first collection of conditional mutant alleles outside the mouse; unlike popular mouse conditional alleles that are switched from "on" to "off," zebrafish mutants conditionally go from "off" to "on," offering new insight into localized gene requirements. The transposon system results in fluorescence-tagged mutant chromosomes, opening the door to an array of new genetic screens that are difficult or impossible to conduct using more traditional mutagenesis methods, such as chemical or retroviral insertion.

The project also marks the first in vivo mutant protein trap in a vertebrate. Leveraging the natural transparency of the zebrafish larvae lets researchers document gene function and protein dynamics and trafficking for each protein-trapped locus. The research also ties gene/protein expression to function in a single system, providing a direct link among sequence, expression and function for each genetic locus.

Researchers plan to integrate information from this study into a gene codex that could serve as a reference for information stored on the vertebrate genome.

Shedding Light on Disease

Researchers exposed translucent zebrafish to transposons, "jumping genes" that move around inside the genome of a cell. The transposons instructed zebrafish cells to mark mutated proteins with a fluorescent

protein 'tag.'

"This makes investigation of a whole new set of issues possible," Dr. Ekker says. "It adds an additional level of complexity to the genome project."

Dr. Ekker's team maintains about 50,000 fish in the Zebrafish Core Facility. To observe, photograph and document mutations of that many minnow-sized fish, the team works with an international team of researchers and gets helps from Rochester public elementary school teachers. Under a program with Mayo Clinic and Winona State University called InSciEd Out (Integrated Science Education Outreach), teachers document mutations and learn about the scientific method.

Provided by Mayo Clinic