Study gives clue as to how notes are played on the genetic piano

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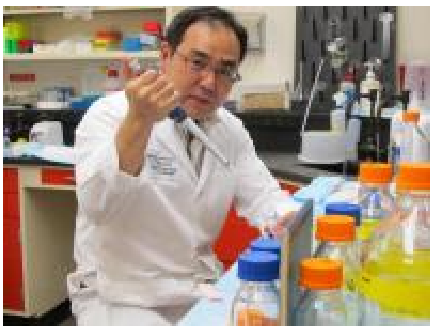

Dr. Kohzoh Mitsuya, of the School of Medicine at the University of Texas Health Science Center San Antonio, is co-author of a paper in *Science* pointing to an epigenetics rationale for why some genes are silenced and others are not. Credit: UT Health Science Center San Antonio

Japanese and U.S. scientists in the young field of epigenetics Thursday reported a rationale as to how specific genes are silenced and others are not. Because this effect can be reversed, it may be possible to devise therapies for cancer and other diseases using this information.

The *NOVA* U.S. public television program described epigenetics as "The Ghost In Your Genes." It is the study of changes in gene expression that occur without changes in DNA sequence. Like keys on a piano, DNA is the static blueprint for all the proteins that cells produce. Epigenetic information provides additional dynamic or flexible instructions as to how, where and when the blueprint will be used. "It corresponds to a pianist playing a piece of music," said Kohzoh Mitsuya, Ph.D., postdoctoral fellow in the School of Medicine at The University of Texas Health Science Center San Antonio.

The study by Dr. Mitsuya and colleagues is outlined in the May 13 issue of the journal *Science.* The team found that a small RNA pathway is required to establish an epigenetic modification — called DNA methylation — at a gene that codes for mammalian proteins. DNA methylation adds chemical tags called methyl groups to specific genes, usually silencing their expression.

"DNA methylation marks are reversible, so there is great interest in devising therapeutic strategies, for instance in cancer biology, to epigenetically reactivate silenced tumor-suppressor genes or inactivate specific oncogenes in human cancer cells," Dr. Mitsuya, the *Science* paper's third author, said. The lead author is Toshiaki Watanabe, Ph.D., of the National Institute of Genetics in Japan and Yale University.

Beyond being reversible, DNA methylation is susceptible to environmental influences. Many cancer biologists now agree that changes in DNA methylation might be as important as genetic mutations in causing cancer. There are far more epigenetic changes than genetic changes found in the majority of cancers, and research into epigenetics is proving to be important to understanding cancer biology.

"It is critical to identify the entire complement of factors that affect gene silencing," Dr. Mitsuya said. "This was the rationale behind this study examining DNA methylation in mice that I began in 2004. The study adds information about one set of factors."

The researchers compared a group of normal mice with a group lacking the small RNA species. The team found that DNA methylation was markedly reduced at one of four genes tested in the small RNA-deficient mice. "This is the first demonstration that small RNAs can act in this way," Dr. Mitsuya said. "It shows how one note is played on the piano."

Epigenetic activity is a previously unseen dimension of biology that may enable clearer detection of disease, monitoring of progression and improved treatment, and may provide entirely new biomarkers of disease susceptibility. "The symphony has only just come into view," Dr. Mitsuya said. "We can hear it, but we need to learn how all the parts are being played."

More information: Role for piRNAs and Noncoding RNA in De Novo DNA Methylation of the Imprinted Mouse Rasgrf1 Locus. Toshiaki Watanabe, Shin-ichi Tomizawa, Kohzoh Mitsuya, Yasushi Totoki, Yasuhiro Yamamoto, Satomi Kuramochi-Miyagawa, Naoko Iida, Yuko Hoki, Patrick J. Murphy, Atsushi Toyoda, Kengo Gotoh, Hitoshi Hiura, Takahiro Arima, Asao Fujiyama, Takashi Sado, Tatsuhiro Shibata, Toru Nakano, Haifan Lin, Kenji Ichiyanagi, Paul D. Soloway, Hiroyuki Sasaki. *Science* DOI: 10.1126/science.1203919

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