

Nov 30, 6:49 AM EST

Duke Scientists Map 'Silenced Genes'

By LAURAN NEERGAARD
AP Medical Writer

WASHINGTON (AP) -- Remember biology class where you learned that children inherit one copy of a gene from mom and a second from dad? There's a twist: Some of those genes arrive switched off, so there is no backup if the other copy goes bad, making you more vulnerable to disorders from obesity to cancer.

Duke University scientists now have identified these "silenced genes," creating the first map of this unique group of about 200 genes believed to play a profound role in people's health.

More intriguing, the work marks an important step in studying how our environment - food, stress, pollution - interacts with genes to help determine why some people get sick and others do not.

"What we have is a bag of gold nuggets," lead researcher Dr. Randy Jirtle said about the collection of "imprinted" genes. The team's findings were published online Friday by the journal Genome Research.

Next comes work to prove exactly what role these genes play. "Some will be real gold and some will be fool's gold," Jirtle added.

Usually, people inherit a copy of each gene from each parent and both copies are active, programmed to do their jobs whenever needed. If one copy of a gene becomes mutated and quits working properly, often the other copy can compensate.

Genetic imprinting knocks out that backup. It means that for some genes, people inherit an active copy only from the mother or only from the father. Molecular signals tell, or "imprint," the copy from the other parent to be silent.

Jirtle compared it to flying a two-engine airplane with one engine cut off. If the other engine quits, the plane crashes. In genetic terms, if one tumor-suppressing gene is silenced and the active one breaks down, a person is more susceptible to cancer.

Only animals that have live births have imprinted genes. It was not until 1991 that it was proved that humans had them. Until now, only about 40 human imprinted genes had been identified.

The Duke map verified those 40 and identified 156 more. Researchers fed DNA sequences into a computer program that decoded patterns pointing to the presence of imprinted genes instead of active ones.

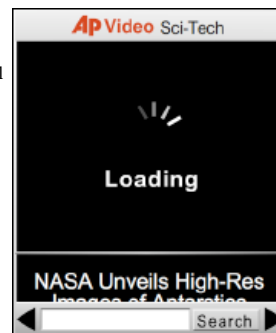
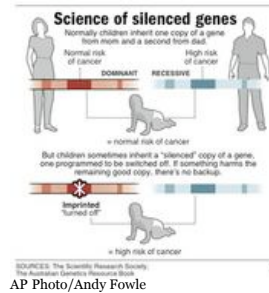
Many of the newly found imprinted genes are in regions of chromosomes already linked to the development of obesity, diabetes, cancer and some other major diseases, the researchers reported. One, for example, appears to prevent bladder cancer. A second appears to play a role in causing various cancers and may affect epilepsy and bipolar disorder.

Scientists had thought imprinted genes would account for about 1 percent of the human genome. While scientists must double-check that the newly identified ones are truly silenced, the new map matches that tally.

"It's a fascinating paper," said Dr. Nora Volkow, director of the National Institute on Drug Abuse. Volkow praised the new mapping method for speeding the slow discovery of these genes.

She said finding which genes are imprinted is important for a bigger question: How do behavioral or environmental factors tip the balance for someone who is genetically predisposed to a health problem?

Previous work by Jirtle and others shows the environment can reprogram how some genes operate, making them speed up or slow down or work at the wrong time. In a groundbreaking 2003 experiment, Jirtle fed pregnant mice different nutrients to alter the coat color of their babies. The feed affected chemical signals that control how hard a certain gene worked, determining when the babies had yellow coats like mom or brown ones.



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"It's not just about the sequence of your genes, but how that sequence is turned on and off by environmental exposures that is likely to determine whether you will be healthy," Volkow said. Imprinted genes "are likely to be particularly susceptible to environmental factors."

Sometimes imprinting goes awry before birth, leaving a normally silenced gene "on" or silencing one that should not be. Faulty gene imprinting leads to some devastating developmental disorders, such as Angelman syndrome, which causes mental retardation.

Now a question is how imprinting may be changed to reactivate an imprinted gene after birth.

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