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RESEARCH NEWS

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Mitochondrial DNA's Surprising Variability Could Complicate Forensic and Genealogical Analyses

Forensic anthropologists, human evolution researchers, and crime scene investigators might want to take note: The mitochondrial genome–long thought to be nearly identical in every cell in the human body–actually varies to a surprising degree, according to new research by Howard Hughes Medical Institute (HHMI) scientists. The research shows that different forms of the mitochondrial genome can be present in different organs from the same individual, and that these forms probably arise during embryonic development.

Mitochondria are the power plants of the cell, and each of these organelles holds several copies of its own genome, a circle of DNA about 16,000 base pairs long. Human mitochondria are almost always inherited from the mother, and so mitochondrial DNA has been used to trace maternal ancestry. Mitochondrial DNA makes up only a tiny fraction of the total amount of DNA in human cells, yet because each cell in the body holds anywhere from 50 to several hundred mitochondria, each mitochondrial gene is present in much greater abundance than genes in the cell's nucleus. The relative abundance of mitochondrial DNA has made it a powerful tool for forensic scientists, who use it to match suspects to human blood or tissue samples retrieved from crime scenes.

New data from the lab of HHMI investigator Bert Vogelstein may push scientists to reconsider how they employ mitochondrial DNA. "The bottom line is there is no single mitochondrial genome in humans," says Vogelstein. "We were surprised to find how much the DNA of mitochondria varies within each individual."

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Vogelstein, who studies colon cancer at the Kimmel Cancer Center at Johns Hopkins University School of Medicine, began studying mitochondrial DNA because he was interested in using it as a tool to track whether tumors recurred after treatment. Mitochondrial DNA is attractive as a diagnostic tool for the same reason it is used in forensics: mutations indicating the presence of a tumor are easier to find if they are present in many copies. About a decade ago, scientists in Vogelstein's laboratory discovered that mitochondrial DNA inside tumors carried telltale genetic mutations that could be used to signify the presence of colon cancer. Vogelstein wanted to develop a blood test to search for these mutations, reasoning that such a diagnostic would help clinicians detect the presence of residual cancer after surgery or other treatments. This information could help clinicians decide when or whether to begin additional therapy.

Previous studies of mitochondrial DNA suggested that the billions of mitochondrial genomes within each individual were largely identical. But those studies used DNA sequencing techniques that are not sensitive enough to detect differences in DNA sequence that occur infrequently. In the current study, which was published in the March 4, 2010, issue of the journal *Nature*, Vogelstein deployed highly sensitive next-generation DNA sequencing technologies. The technology allowed Vogelstein and his colleagues to find single-letter DNA changes that occur in as few as 1 in 10,000 mitochondria.

Starting with the DNA from a colon cancer, the next-generation sequencing technology allowed the investigators to identify several variations in mitochondrial DNA. To see if these variations were tumor-specific, Vogelstein's team sequenced mitochondrial DNA from healthy colon tissue from the same patient. Again, they found many variations in the mitochondrial DNA sequences, much more than they expected.

Next, the team studied 10 different tissue types from a single individual. They found that mitochondrial DNA sequences varied from tissue to tissue. However, occasionally two different types of tissue – such as kidney and liver –contained the same variation.

To sort out the source of these variations, Vogelstein's team in Baltimore contacted researchers at the Centre d'Etude du Polymorphisme Humain in France to obtain white blood cells from the parents and two children in each of two different families. In both families, Vogelstein found that mitochondrial DNA variants from the father were not passed to the children, meaning that – as expected -- sperm cells were not the source of any variation. However, in one family, the mother passed two telltale mitochondrial DNA variants to her children. In both mother and child, the variant appeared in about 56 percent of all mitochondria. This suggested to Vogelstein and his colleagues that the oocyte that eventually developed into the child contained mitochondria with slightly different genomes.

However, the total variation in the mother's mitochondrial DNA was too low to account for the wide variation seen in the earlier sequencing. That led the scientists to conclude that most of the variants arose spontaneously during early embryonic and fetal development. That origin would explain why the same variant sometimes appears in two tissues: the variation arose very early in development, before the two tissues differentiated from each other.

“Mutations in mitochondrial DNA are apparently occurring all the time, but only the variants that are locked in during early development occur at a high enough frequency for to be detected by the techniques we used,” says Vogelstein.

The implications for forensic science are clear. Right now if the mitochondrial DNA from a crime scene sperm sample does not match the mitochondrial DNA from a suspect’s cheek swab, the suspect is ruled out as the perpetrator. But Vogelstein’s work shows that even if the mitochondrial DNA from two tissues doesn’t precisely match, it might still be from the same individual. “Forensic scientists should be cautious when excluding suspects on the basis of mitochondrial DNA evidence,” says Vogelstein.

As for mitochondrial DNA’s utility in tracking tumors, Vogelstein and his colleagues found that mutations specific to colon tumors can be found in tiny blood samples, and that the signature of those mutations vanished after the tumor was removed surgically. Vogelstein says that ongoing research will show whether such tests can also predict cancer recurrence.