Tiny molecule can be a powerhouse in some investigations, problem in others

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By RACHEL EHRENBERG / The Dallas Morning News

When the Army exhumed the brother of murdered Czar Nicholas II, nobody expected to find much ordinary DNA to analyze. This molecular fingerprint decays quickly, and the remains had been buried for nearly a century.

But the body's cells host a second type of DNA, one that is abundant enough that some survives even when all that is left are bones and teeth.

In the past decade, this "mitochondrial" DNA has become an important tool in forensic science, helping identify human remains from the World Trade Center rubble, for example, and providing clinching evidence in courtrooms.

But as scientists learn more about this smaller, humbler molecule, they're finding its use in forensics poses some problems, too.

The specific chemical arrangement, or profile, of mitochondrial DNA is rarely unique. For one thing, the molecule's size is limiting. Like a combination lock with only a few numbers, there isn't much room for variation.

Also, a single person can have more than one mitochondrial profile, confounding investigations.

"There is a lot more to learn about this molecule and its importance in human biology," says Doug Wallace of the University of California, Irvine. "We need to know about that biology before we can be certain about its predictive use as a forensics tool."

As long as analysts are aware of the molecule's forensic shortcomings, mitochondrial DNA can continue to provide a lot of useful information, says Thomas Parsons, chief scientist of the U.S. Army's DNA identification laboratory. Mitochondrial DNA is shedding light on how and where human beings evolved. It's used to track missing persons and identify war victims from Argentina to Croatia. And while its quirks can complicate the interpretation of evidence, they can also strengthen its punch.

A dynamic duo

Most of the time, regular old DNA is the forensics molecule of choice, says Dr. Parsons. You inherited this DNA 50-50 from your parents, and it's nicely arranged into chromosomes in each cell's nucleus. This "nuclear" DNA is the master copy of directions for making almost everything in your body – including portions of the mitochondria, the factories in the body's cells that turn sugars into energy.

By the mid-20th century, scientists understood that mitochondria always spring from pre-existing mitochondria. But not until the late 1960s did they realize mitochondria have their own DNA, which governs production of the rest of the mitochondrial machinery. This led many biologists to suggest the factories were once independent, single-cell creatures that took up residence in other cells.

Like a blue-collar cousin, mitochondrial DNA doesn't have the nice packaging of nuclear DNA. It isn't wrapped in proteins or tended to and repaired by other molecules in the...
The mitochondrial DNA molecule – just a small ring, like two tiny rubber bands twisted together – provides blueprints only for the body’s small cellular factories plus a few proteins.

It is one-300,000th the size of regular DNA. But it is much more plentiful.

The sheer quantity of mitochondrial DNA is what makes it such a useful forensics tool, says Dr. Parsons. And sometimes it’s all that’s available, such as when the only physical evidence is white blood cells or naturally shed hair with no follicle attached.

With rare exceptions, only mothers pass mitochondrial DNA on to their kids, for reasons scientists are still trying to figure out. There isn’t any mixing up of genetic material as there is in the cell’s nucleus with the DNA that’s inherited from both parents. Most of the time, all of your mitochondrial DNA is just like that of your siblings, your mother, her mother – your whole maternal lineage.

The molecule’s small size, and the fact that it doesn’t tango with your father’s DNA, means that it is very unlikely that your mitochondrial DNA profile is unique. Nuclear DNA is divvied up into 23 chromosomes (plus a Y chromosome for men), each like an individual combination lock with many more numbers than your lone, small, mitochondrial lock. Since the odds of having a unique combination are much smaller with mitochondrial DNA, it’s harder to say with certainty that a particular sample came from a particular person.

"Unlike nuclear [DNA] typing, where you can say one in a trillion have this DNA, with mitochondrial DNA you go into the database and say I have one match in 5,000, so you cannot say it is definite, but one in 5,000 is uncommon," says Ranajit Chakraborty of the University of Cincinnati, an author of a recent overview of mitochondrial DNA in forensics in the Annual Review of Human Genetics.

"What it boils down to is how common or rare is the type shared between the suspects and the sample," says Dr. Parsons.

Still, because mitochondrial DNA provides a maternal bar code, the molecule is vital in missing persons investigations. Samples taken from any maternal relative might be compared with the mitochondrial DNA extracted from a bone fragment at a burial site. Mitochondrial DNA is helping families find relatives lost to war in Argentina, Bosnia and Herzegovina.

"It is a great tool when you have disasters like the World Trade Center, or the way that the Army’s using it to identify missing relatives," says evolutionary biologist Bill Shields of the State University of New York College of Environmental Science and Forestry in Syracuse.

The Army’s DNA identification lab, which dealt with the Sept. 11 victims’ remains from Shanksville, Pa., and the Pentagon, was established in 1991 for analyzing remains of U.S. soldiers killed in battle. The lab has identified more than 75,000 soldiers from World War II and thousands more from Vietnam and Korea, mostly using mitochondrial DNA from bones and teeth. In one notable case, the lab identified the remains of the Vietnam War soldier buried in the Tomb of the Unknowns.

Change leaves its mark

As with all DNA, mitochondrial DNA can become damaged or mutated in any number of ways; it is these accumulated changes that scientists analyze. Generally, these changes pile up very gradually. But scientists are finding that someone’s mitochondrial bar code can change over the course of a lifetime.

Mitochondrial DNA can’t repair itself like regular DNA, so if damage to the molecule is severe, the cell will probably self-destruct. But if the alterations aren’t in a crucial part of the genetic instructions, they might not shake things up too badly – so those alterations are passed on when more mitochondria are made from the same mutated molecule.

"If you are looking at different tissues in the same individual, or looking at different points in time, the molecule can change," says Pinar Coskun, a colleague of Dr. Wallace’s and an author of a recent paper in the Proceedings of the National Academy of Sciences exploring mitochondrial DNA’s complexities. "That can give you a hard time when you are deciding who a sample really belongs to."

Several genetic disorders have been traced to mitochondrial DNA mutations, including Leber’s disorder, a rare form of blindness that sets in at adolescence. Dr. Coskun is on the trail of a mutation that may be linked to Alzheimer’s disease.

Mothers pass a handful of mitochondrial DNA molecules onto their children, so if your mom’s profile changed during her lifetime, you can inherit more than one. This can lead to whole tissues or organs that have a different DNA signature than other parts of the body – your hair, for example, might have different mitochondrial DNA than your blood. (And in one case described last
year, a man had actually inherited his father's mitochondrial DNA in his muscle tissue.)

"Each individual is sort of its own population," says molecular anthropologist Mark Stoneking of the Max Planck Institute for Evolutionary Anthropology, so having more than one profile isn't outrageous. Five to 10 DNA molecules are in each mitochondrion, and most cells teem with hundreds to thousands of the little factories.

"And we are made up of trillions of cells," says Dr. Stoneking. "In a way, it is surprising that there is so much consistency."

Ethnic distributions

About 10 percent to 15 percent of the individuals surveyed by Dr. Stoneking's lab have more than one type of mitochondrial DNA. His work focuses on how mitochondrial DNA is distributed among populations and ethnic groups. The mitochondrial DNA pool of people from India, for example, is more similar to people from Eastern Europe and Asia than to western Europeans, he and his colleagues reported this spring in the European Journal of Human Genetics.

Mitochondrial DNA's skewed distributions in different populations are another cause for caution in the courtroom, says Dr. Shields. In a recent case, he found that the suspect's mitochondrial DNA matched 10 of the 4,000 signatures in the database – equaling one match in 400, and suggesting the profile wasn't very common. But a closer look revealed that all 10 hits were within the 90 samples from Japanese individuals, meaning that one in nine Japanese might have the same profile. Though rare in the database, the signature was not actually rare among people of Japanese heritage.

"It is crucial that the 'mito' DNA isn't looked at in the context of the entire community, but in the local community," says Dr. Shields. "And in any city that has ethnic diversity, all ethnic groups must be represented in the database."

While expert witnesses are usually aware of the molecule's limitations, the same can't be said for other players in the legal system, says Dr. Shields, who has testified in numerous cases involving mitochondrial DNA, including the first U.S. court case in 1996.

"The prosecutors and the defense attorney are free to interpret it as they want – I've heard an attorney say, 'This mitochondrial DNA came from that man!' That might be OK legally, but scientifically it is ludicrous," he says.

Experts must use appropriate statistics, says Dr. Shields, so the meaning of "matching samples" is clear. The best-case scenario is comparing known information – as when unidentified remains could be traced to only a handful of people, and there are known relatives of each for comparison.

Such was the case with Nicholas II's brother. In the early 1990s, a team of forensic scientists unearthed the purported remains of the Russian czar, his wife and some of their children from a shallow grave outside the Siberian town of Ekaterinburg. Political enemies shot and killed the family in 1918 and, after trying to burn the bodies, buried them in the woods. Even though all of the forensic evidence suggested the remains were those of the royal family, when the czar's mitochondrial DNA was compared with that of a distant maternal relative, it didn't quite match.

When the forensics lab took a closer look at the czar's DNA, they realized he was a rare individual who had two mitochondrial profiles, and one matched the DNA of his distant relative.

This was one of the first instances of multiple profiles in a forensics case, and the Russian government wanted more verification. So in 1996, the U.S. Army's forensic lab, working with the leading forensics lab in Russia, exhumed the remains of Czar Nicholas II's brother, Georgij Romanov, to see whether he shared the dual signatures.

Romanov had been dead since 1899, and his coffin had been flooded with water for at least 60 years. Nonetheless, the labs got their DNA and with it, their man.

"When the brother's DNA came rolling off and it was a match," says Dr. Parsons, "you knew in a heartbeat. You'd gone from having a complicating conundrum to something that hits the nail on the head."

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