Biology

DNA test confirms dead czar's identity

A new genetic analysis may finally allow former Russian Czar Nicholas Romanov II to rest in peace. On the night of July 16, 1918, a firing squad of Bolshevik soldiers executed the Russian royal family, including Nicholas, and buried the bodies in a hidden mass grave. The burial site finally came to light in 1989, and 2 years later nine skeletons were excavated.

Though forensic analyses of the bones, clothing, and other material from the grave have provided strong evidence that some of the skeletons belonged to the czar and his family, attempts to confirm the identifications by analyzing DNA samples have provoked controversy. When researchers compared DNA from bones presumed to be those of Nicholas II with DNA from two living relatives, they found an unusual mismatch.

DNA is composed of long sequences of building blocks called nucleotides, which come in four forms that geneticists label A, C, G, and T. The bits of DNA from the skeleton and Nicholas II's relatives matched perfectly except at one position. At a nucleotide site where both living relatives had a T, some of the DNA samples from Nicholas' bones had a T but others had a C. Such variation is a rare condition called heteroplasmy.

Despite the difference, investigators proclaimed that Nicholas had been identified. Yet the Russian Federation government and the Russian Orthodox Church, which is considering canonizing the entire Romanov family, demanded further proof. In July 1994, researchers resorted to exhuming the body of Georgij Romanov, Nicholas' younger brother, who had died of tuberculosis in 1899.

Like Nicholas's DNA, Georgij's had either C or T present at the controversial site, report Pavel L. Ivanov of the Russian Academy of Sciences in Moscow and a team from the Armed Forces DNA Identification Laboratory in Rockville, Md., led by Thomas J. Parsons. The team describes its findings in the April NATURE GENETICS. The heteroplasmy, says Parsons, must have disappeared somewhere in the generations after Nicholas.

An editorial in NATURE GENETICS notes that this is the first time heteroplasmy has been used to aid identification. "To me, this is the nail in the lid. It's the most convincing argument I've seen," adds William R. Maples of the University of Florida in Gainesville, who had suggested earlier that Nicholas' apparent heteroplasmy resulted from contamination of the DNA samples.

Fishing around for the right mate

Finding the right male to mate with is not a simple matter—not even for a female guppy. Oh sure, she could go just for good looks: a guy's size, tail length, and color, for example. Some of these physical preferences are so important to reproduction that they appear to be hard-coded into a guppy's genetic heritage.

Yet female guppies don't depend solely on those factors for choosing a mate, notes Lee Alan Dugatkin of the University of Louisville in Kentucky. A few years ago, he found that a female guppy often imitates the mating choices of other females.

In the April 2 PROCEEDINGS OF THE NATIONAL ACADEMY OF SCIENCES, he reports on the first systematic look at whether appearance or cultural cues dominate this fishy issue. He finds that female guppies, which normally prefer a mate with lots of orange, are easily persuaded to pick a male with less orange coloration if they observe another female mating with him.

In special cases, looks can override those cultural cues. "When the males are dramatically different [in amount of color], females don't copy," says Dugatkin. If one of two available males has at least 40 percent more orange color than the other, a female will mate with him regardless of the other females' actions. Dugatkin suggests that examining the behavior of guppies may provide insight into how to study the inherited and cultural factors that govern mating choices of women.

Biomedicine

Tuberculosis gene may explain dormancy

The tuberculosis bacterium is nothing if not an artful dodger. Over the years, it has proved itself capable of eluding almost every trap mankind has laid. Now, researchers have gained an important insight into an ancient conundrum—how the tuberculosis microbe manages to remain dormant in the lungs for years before flaring up into active disease.

Not surprisingly, the secret appears to be genetic. Tuberculosis contains a gene called *SigF*, which regulates dormancy, report William R. Bishai of Johns Hopkins School of Hygiene and Public Health in Baltimore and his coworkers. When the bacterium is under stress, as it is in the hostile environment of the lungs, *SigF* may enable it to sporulate, or turn itself into a seed, in order to protect itself, says Bishai. This gene resembles sporulation genes identified in other bacteria.

Doctors had discarded sporulation as a possible explanation for tuberculosis' remarkable staying power because no one has ever successfully coaxed the bacterium to form spores in the lab. But that doesn't mean it can't happen in the body, say Bishai and his coworkers in the April 2 PROCEEDINGS OF THE NATIONAL ACADEMY OF SCIENCES.

"In all honesty, we were hoping to find something like this," Bishai says. "We didn't expect to find a sporulation gene first off. That was exciting."

The presence of the gene is not proof of its activity, however, says Bishai, adding that no one has retrieved latent microbes from an infected individual. The key step involves destroying the *SigF* gene—a challenge in itself—to see whether this affects the bacterium's ability to become dormant.

If the gene functions as Bishai and his coworkers hypothesize, the finding could hold important implications for treatment. "Suppose we could develop drugs that affect the shift to dormancy?" Bishai asks. If scientists could manipulate the bacterium's life cycle, "we could treat infections for shorter periods. We could [treat] multidrug-resistant TB simply by putting the [microbes] into a dormant state."

Researchers might also be able to develop a vaccine strain simply by knocking out the *SigF* gene, Bishai says. Without the gene, the bacterium theoretically would lose its ability to protect itself against the immune system—unless, of course, the artful dodger has a new trick up its sleeve.

Cystic fibrosis: An antibiotic cure?

Cystic fibrosis, a lethal, inherited respiratory disease, has flouted attempts at treatment—even gene therapy. Now, an antibiotic commonly used to treat infection in cystic fibrosis patients may combat the illness itself in some patients.

The antibiotic, an aminoglycoside, can overcome the genetic defect that causes cystic fibrosis in 5 percent of patients, according to David M. Bedwell of the University of Alabama at Birmingham and his coworkers. They report their findings in the April NATURE MEDICINE.

The genetic defect involves the *CTFR* gene. In some people with cystic fibrosis, the gene has abnormalities, called stop mutations, that derail the process of producing the CTFR protein. Lacking that protein, cystic fibrosis patients cannot clear the disease's characteristic thick mucus out of their lungs.

The researchers, building on earlier work showing that aminoglycosides can override stop mutations, exposed damaged *CTFR* genes to the antibiotic in the lab. They found that the damaged genes produced functioning protein when bathed in the antibiotic.

Ironically, though doctors have routinely prescribed aminoglycosides to combat infections in people with cystic fibrosis, they stop offering the antibiotic when the infection clears. In some patients, continuing the therapy may provide long-term relief from cystic fibrosis itself, Bedwell says.

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