Closing in on the Lou Gehrig's disease gene

A team of neuroscientists has identified a gene that when damaged may cause the inherited form of amyotrophic lateral sclerosis (ALS), or Lou Gehrig's disease—a devastating, ultimately fatal neurodegenerative disorder with no effective treatment.

If confirmed by further studies, the finding may pave the way for the development of therapeutic drugs for both the inherited and the noninherited – or sporadic – forms of ALS, which together strike roughly one in every 100,000 individuals worldwide.

The research team, led by James O. McNamara of the Duke University Medical Center in Durham, N.C., has found that a gene which codes for part of a key nerve-cell receptor lies within the same region of chromosome 21 as that known to become damaged in the inherited form of ALS. Taken together with previous research findings related to ALS, McNamara asserts, the new evidence suggests that mutations in the gene cause the inherited form of the disorder.

ALS results from the gradual death of nerves in the lower brain and spinal cord that control movement. Most ALS patients develop the initial symptoms, including muscle stiffness and weakness, in their forties or fifties. Eventually, the disorder disables the body's muscles, and patients usually die within five years from respiratory failure.

From studies of families with multiple members affected by the disorder, researchers estimate that between 5 and 10 percent of ALS cases have a genetic cause. In the mid-1980s, some scientists began to suspect that the nerve-cell death in ALS arises from mutations impairing the cells' ability to properly use glutamate, one of the chemicals that transfers messages between nerve cells.

Laboratory studies showed that high concentrations of glutamate can kill nerve cells by causing them to take up toxic levels of calcium. Moreover, epidemiologists identified a glutamate-like compound as the cause of the high incidence of an ALS-like disease in Guam. Other scientists discovered that the same compound can prompt calcium-related nerve damage when fed to monkeys.

McNamara – who also holds an appointment at the Department of Veterans Affairs Medical Center in Durham – and his colleagues have now added to these previous findings by isolating the gene that codes for one subunit of the receptor that responds to glutamate by allowing calcium to enter a nerve cell. In the Jan. 1 PROCEEDINGS OF THE NATIONAL ACADEMY OF SCIENCES, the researchers suggest that mutations in the gene lead to the production of faulty receptors, which permit too much calcium to enter the cell when triggered by glutamate.

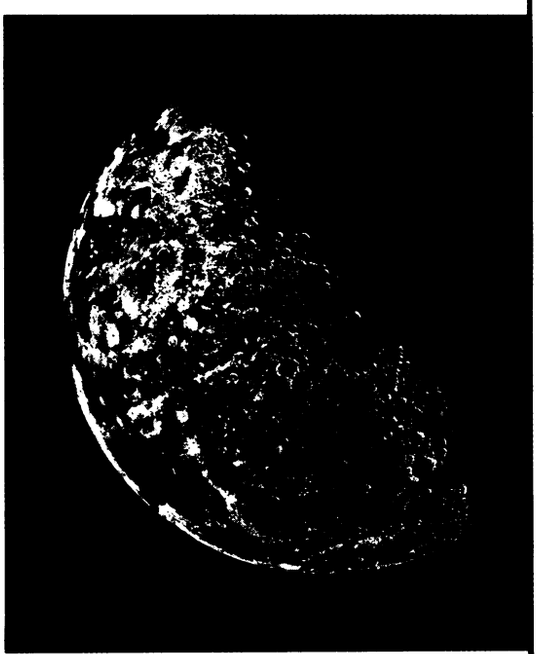
McNamara asserts that the faulty-receptor theory might explain why the symptoms of ALS develop only later in life. Each defective receptor might take up just a bit too much calcium, he suggests, leading to a slow but steady calcium buildup that eventually proves fatal to a nerve cell years later.

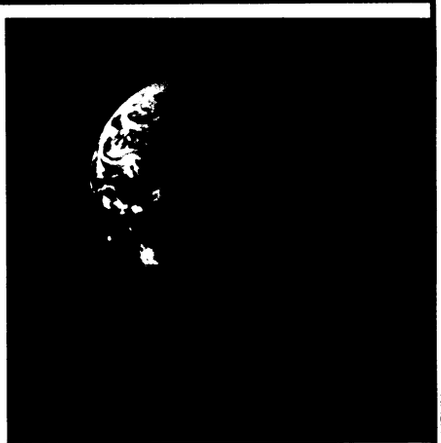
The same nerve-destroying process might occur after the gene for the glutamate receptor subunit becomes damaged by environmental insults, McNamara says, leading to the sporadic form of ALS. "By understanding the genetics . . . we may shed light on the mechanisms involved in the sporadic form," he says.

"This is a very good candidate gene for ALS," comments Allen D. Roses, a neuroscientist at Duke who did not participate in the new study. However, he says that researchers must perform further experiments to determine the role of the glutamate receptor subunit gene in the disorder, such as splicing a defective copy of the gene into nerve cells to see if it makes them accumulate calcium and die.

Both McNamara and Roses agree that the advance, if confirmed, could lead to a treatment for ALS by providing a target for drug therapy. "If this is the gene, drugs to block the [defective] receptors would be a rational approach to therapy," Roses says. *– C. Ezzell*

Galileo gathers views of Earth and moon





NASA

The Galileo spacecraft swung by Earth last month, receiving from the planet a second and final gravitational kick on its way to orbit Jupiter in 1995. Flying over the moon and recording images of the lunar north pole at several different wavelengths – a feat never before accomplished – Galileo found evidence that the moon was more volcanically active during its early history than researchers had thought.

On Dec. 7, the craft gathered a variety of infrared and visible-light fingerprints that indicate the chemical composition of the moon's polar region. In the false-color image at top right, which NASA released Dec. 22, pink denotes highlands; blue and orange indicate volcanic lava flows; and light blue indicates thin, mineral-rich soils associated with relatively recent meteorite impacts.

The picture suggests that these and other impacts on the moon have exposed lava flows more than 3 billion years old. The size of the lava flows indicates that the moon had even more frequent and extensive volcanic disturbances during its youth than suspected, says Jay Bergstralh, Galileo program scientist at NASA in Washington, D.C. In an image taken eight days later (bottom right), the craft captured the Earth and the far side of the moon.

Because Galileo's main antenna remains jammed, researchers have only just received the final data from the craft's encounter with the asteroid Gaspra in October 1991. Near its closest approach, the craft found indirect evidence of a magnetic field surrounding Gaspra: The solar wind changed direction a few hundred kilometers from the asteroid, as if it had slammed into a magnetic region. The magnitude of the inferred magnetic field appears similar to that associated with iron-rich meteorites – possible fragments of asteroids like Gaspra – that have fallen to Earth, reports Margaret G. Kivelson of the University of California, Los Angeles.