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Mouse Coat-Color Gene Mutation Mimics Neurodegeneration of Prion Diseases

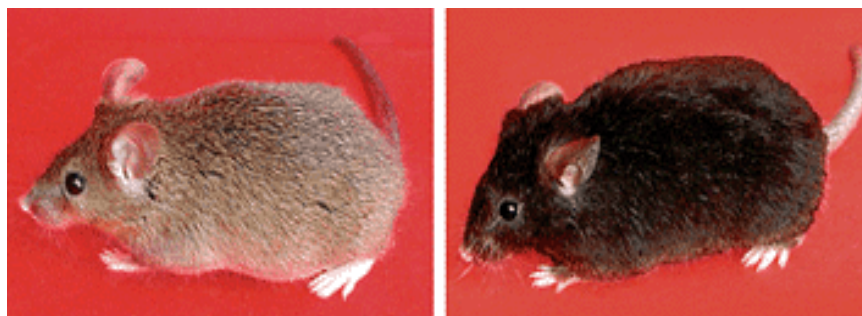


Image Title: The photos show a normal mouse (left) and a *mahoganoid* mouse whose characteristic black coat color is caused by a genetic mutation that also causes degeneration of neurons. - Laboratory of Gregory Barsh/HHMI at Stanford

Howard Hughes Medical Institute researchers have found that a gene mutation that produces a black coat color in mice also causes degeneration of neurons similar to that observed in prion-caused diseases, such as Creutzfeldt-Jakob disease and “mad cow disease.” The scientists say that their findings could improve understanding of how the renegade proteins, called prions, destroy the brains of infected humans, cattle and sheep.

In an article published in the January 31, 2003, issue of the journal *Science*, researchers led by Howard Hughes Medical Institute investigator Gregory Barsh at Stanford University reported that a gene mutation in *mahoganoid* mice causes neural damage that closely resembles that observed in spongiform encephalopathies. The work was carried out by Lin He and Teresa Gunn, graduate student and former postdoctoral fellow with Barsh, respectively, and also involved collaboration with the University of Michigan School of Medicine.

Gunn, He, and Barsh began looking at the effects of *mahoganoid* mutation on neural development after their studies of another mutation in a similar coat-color gene, called *Attractin*, turned up some intriguing results.

“Both gene mutations have been recognized as coat-color mutations for decades,” said Barsh. “In the last few years, our group and others recognized that *Attractin* mutations affected not only hair color but also caused neurodegeneration with a phenotype very similar to that caused by the prion diseases.” Unlike the prion-produced diseases, the genetic malfunctions in *Attractin* are not transmissible, do not involve an abnormal prion protein and are not as rapidly lethal, Barsh noted.

The *Attractin* and *mahoganoid* mutations appeared to be in the same genetic pathway that governs coat-pigment production, so the researchers reasoned that the *mahoganoid* mutation might also produce neurodegeneration. Indeed, when the scientists examined the brains of *mahoganoid* mice, they found the same pathology.

“In *mahoganoid* mice, the changes in the brain occur slightly later than in the *Attractin* mice,” said Barsh. “But they do include the same loss of neurons in the brain's gray matter, accumulation of supporting cells called astrocytes, and small vacuoles. These vacuoles appear initially in the deep part of the cortex and then progress to affect almost all parts of the brain.”

After Gunn, He, and Barsh identified how *mahoganoid* mutations affected the brains of the mice, they began to search for the malfunctioning gene. The researchers constructed a high-resolution genetic map that aided in narrowing their search to a region of the genome containing about 30 genes. Through additional genetic analyses, the scientists pinpointed the abnormal gene and showed that it appeared to be a member of the machinery in the cell that destroys unwanted proteins. The gene, which the researchers named *Mahogunin*, encodes a protein that attaches molecular tags called ubiquitins to other proteins to mark them for destruction.

“It was satisfying to find that the gene that was mutated in *mahoganoid* had a biochemical activity that could help explain the pathophysiology of the neurodegeneration that we were seeing,” said Barsh.

Further experiments revealed evidence that the *Attractin* protein—which is a receptor-like protein—might somehow act as a regulator of *Mahogunin*, both in the pigmentation and neural pathways. “Our findings suggest a potential model whereby *Attractin* either activates or is required for the activity of *mahoganoid*,” said Barsh.

More broadly, Barsh said, the findings implicate this pathway in spongiform degenerative diseases. “Defects in protein metabolism and in the ubiquitin pathway are well known causes of other neurodegenerative diseases like Huntington's disease or Parkinson's disease, but have not previously been implicated in spongiform encephalopathies,” said Barsh. “Our findings suggests the possibility that defects in the ubiquitin pathway play important roles for all of the spongiform encephalopathies—not only the *Attractin-mahoganoid* animals but also the prion diseases.

“Even though it is known that accumulation of abnormal forms of prion protein are the critical event in the development of prion diseases, it is not at all clear how the accumulation of those abnormal proteins leads to the neurodegeneration and neuronal cell death. Our observations that *mahoganoid* defects in the ubiquitin pathway can lead to neuronal cell death that is pretty much indistinguishable from that found in prion diseases suggests that both groups of diseases may proceed by a similar pathway,” said Barsh.

The researchers' studies also demonstrate the value of animal models of disease. “This is a reminder that model systems to study basic questions in cell biology and cell signaling can be applied to a wide variety of important problems in human disease,” Barsh said. “For example, the coat-color system that we study is useful because much is known about the cells and genes involved in pigmentation, and one can use it to measure very subtle changes in gene expression. That is, one can generate mutations and analyze them efficiently much the same way that people do with invertebrate model genetic systems such as flies or worms.”