Cystic fibrosis gene and protein identified

After years of searching through DNA strands, a U.S.-Canadian research team has located the defective gene causing cystic fibrosis and has isolated its protein product. The finding might ultimately lead to new treatments and better genetic counseling for this devastating genetic disorder, which strikes one in every 2,000 white children in the United States.

"There has been an enormous bottleneck in the understanding of cystic fibrosis, and that has been the failure to identify the gene," Francis S. Collins of the University of Michigan in Ann Arbor said last week at a press conference in Washington, D.C. Collins and colleagues Lap-Chee Tsui and Jack R. Riordan of the University of Toronto will publish three scientific papers describing the mutant gene's exact location and protein product in the Sept. 8 SCIENCE.

"There is still a tremendous amount of work to do, but this is a major step forward," says Judith E. Fradkin of the National Institute of Diabetes and Digestive and Kidney Diseases.

Tsui narrowed the search to chromosome 7 in 1985, and the collaboration with Collins yielded a faster method of scanning DNA, enabling the team to pinpoint the faulty gene in March. There they found a mutation resulting in a flawed protein that causes most, though not all, cystic fibrosis cases. The mutant gene's blueprint directs cells to produce a protein missing an amino acid called phenylalanine. "This error somehow changes the ability of the protein to work correctly in the cell," Collins says.

The protein belongs to a class of compounds normally involved in transporting ions, such as sodium and chloride, across cell membranes. Scientists believe cystic fibrosis patients have difficulty moving salt and water in and out of cells, leading to the secretion of thick mucus that clogs airways and leaves patients vulnerable to chronic lung infections.

Riordan says the work may eventually yield drugs that correct the flawed protein's action, thus alleviating the symptoms of cystic fibrosis. But before researchers can look for drugs to compensate for the defect, they must learn precisely how the flawed protein causes the disease, he adds. Alternatively, scientists may find a way to insert a normal gene into the cells of cystic fibrosis patients, directing the cells to manufacture a normal protein product.

Such breakthroughs remain distant, the scientists caution. "Human gene therapy is a new area of investigation, and many scientific, ethical and safety issues must be settled before trying such treatments," Collins says.

Doctors have no treatment now to correct the disease's underlying defect. Instead, they rely on physical therapy to clear away mucus and on antibiotics to combat lung infections. While that regimen has helped prolong lives, most people with cystic fibrosis die by age 30.

With the gene and its protein product identified, says Robert K. Dresing, president of the Cystic Fibrosis Foundation in Bethesda, Md., "we can finally look into the eyes of the children and young adults with cystic fibrosis and tell them that the door to their future has been opened." Dresing has a son with the disease.

In the near term, Collins and his colleagues predict development of a cystic fibrosis screening test for the general population. Currently, genetic counselors can give couples with a family history of cystic fibrosis an estimate of their risk of having a child with the disease, but they have no way to identify healthy carriers of the defective gene who have no such history. One out of 20 whites in the United States carries this genetic flaw but has no symptoms of the disease. To get cystic fibrosis, a child must inherit a defective gene from each parent.

The research team hopes to find other mutations on the same gene within the next few months. At that point, they say, scientists could devise a highly accurate genetic test for cystic fibrosis, including a diagnostic test for fetuses. "A large public education effort will be needed to inform people about cystic fibrosis and enable them to make a rational decision about testing" and whether to abort an affected fetus, Collins says. — *K.A. Fackelmann*

Recombinant rodents, human hemoglobin

Borrowing genes from human red blood cells, researchers have created a strain of genetically altered mice whose red cells contain large amounts of functioning human hemoglobin. The work represents the first successful manipulation of an animal's genetic code to produce human hemoglobin, the crimson protein responsible for transporting oxygen throughout the body.

Scientists say the accomplishment will provide the first animal models to test experimental treatments for human hemoglobin disorders such as sickle cell anemia. It may also lead to the use of farm animals as "biofactories" capable of producing large quantities of human hemoglobin that could serve as a cell-free blood substitute compatible with recipients of any blood type. Blood types, such as A, B and O, are a characteristic of red blood cells, not of hemoglobin itself.

Mice, like humans, use hemoglobin to distribute oxygen from their lungs to body tissues. But mouse hemoglobin is very different from human hemoglobin, says Toshio Asakura of the University of Pennsylvania in Philadelphia, who helped create the transgenic rodents. In mice, where the distance from lungs to oxygen-dependent tissues is relatively small, hemoglobin releases its oxygen readily. In larger animals, hemoglobin binds oxygen more tenaciously.

Scientists remain uncertain about what differences account for these varying oxygen-binding properties in different species. Moreover, while researchers have identified several inherited, disease-causing defects in human hemoglobin chains, they remain stymied in their efforts to find laboratory animals that mimic those errors. The new mice, created under the direction of University of Pennsylvania physiologist Richard R. Behringer and described in the Sept. 1 SCIENCE, have already begun to solve these and other problems.

"This is really exciting," says Leland C. Clark Jr., a blood-substitute researcher at the University of Cincinnati. "It opens up some very interesting possibilities."

Among them, say Clark and others, is the possibility of similarly engineering horses or other large animals and periodically drawing their blood to obtain human hemoglobin. Several researchers, including Enrico Bucci of the University of Maryland School of Medicine in Baltimore, have developed ways of cross-linking human hemoglobin molecules into cell-free blood substitutes (SN: 9/26/87, p.200). But their research and its applications have been hindered by a lack of sufficient hemoglobin to work with. "If this technique breaks loose in large animals, the possibilities become really limitless," Bucci says.

More immediately, the work should prove useful to researchers studying hemoglobin-related diseases. Asakura and his colleagues have already come close to creating mice whose blood contains human "hemoglobin S" — the defective hemoglobin that causes sickle cell anemia. At present, researchers have no animal model for testing potential therapies for the disorder or for studying the feasibility of inserting genes for normal hemoglobin production into sickle cell patients.

The gene-altered mice, which produce human hemoglobin, mouse hemoglobin and two kinds of "hybrid" hemoglobins, also offer a living laboratory for studying the basic chemistry of oxygen transport in blood — research that scientists say could someday introduce a new age of "blood doping" that could improve the speed and endurance of racehorses and human athletes. Early findings lead Asakura to predict that researchers may create novel hemoglobins capable of super-efficient oxygen delivery. If so, he says, "we may be able to create a horse that runs 20 percent faster." — *R. Weiss*