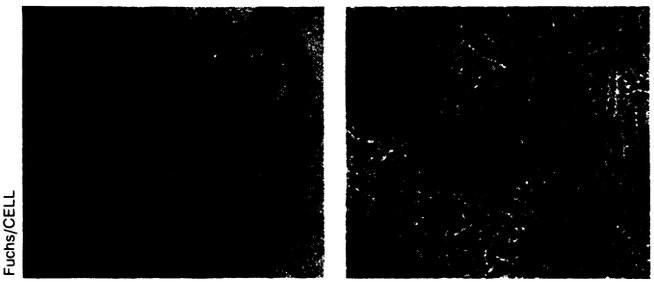
Skin genes underlie blistering disorder



Fuchs/CELL

Long, lacy keratin filaments (far left) normally toughen outer skin cells. One of EB's genetic defects stunts these filaments (left), leaving skin prone to blisters.

They are often born covered with blisters. Their skin is so sensitive that even a mother's loving touch can raise fluid-filled welts. Children with the most severe form of this rare genetic disorder sometimes even lose fingers and toes to the thick scar tissue that forms as the blisters heal.

Epidermolysis bullosa (EB) afflicts an estimated 50,000 people in the United States. For now, treatment is limited mainly to bandages and antibiotic ointments, which help shield the delicate skin and protect the blisters from infection (SN: 1/26/85, p.58; 5/17/86, p.318). But three research reports, uncovering the genetic defects responsible for two types of EB, may offer clues to new treatments – and perhaps a cure – for those who inherit this dire disorder.

Scientists have identified 23 types of EB. Two of the new reports focus on EB simplex, blaming it on a genetic defect in keratin – the key protein in the springy "inner skeletons" of cells. A third report links dominant dystrophic EB, the most severe form, with a damaged gene for collagen, another structural protein.

The new work represents "a tremendous step forward" in understanding EB, says Miriam Feder, executive director of the Dystrophic Epidermolysis Bullosa Research Association of America, based in New York City. "It opens the door to finding a cure," she says.

In the Sept. 20 CELL, researchers report finding similar mutations in the keratin genes of two unrelated EB simplex patients. When they isolated the mutant gene and spliced it into healthy, keratin-producing skin cells called keratinocytes, it disrupted the cells' normal, filamentous internal scaffolding. And when they inserted the gene into bacteria, the microbes produced defective keratin lacking the ability to assemble into long, helical filaments in a test tube.

The investigators, led by Elaine V. Fuchs of the Howard Hughes Medical Institute at the University of Chicago, conclude that the mutant keratin causes blisters by weakening keratinocytes so that they sometimes dissolve when touched. They suggest that the various types of EB arise from "different ... mutations in different regions" of the keratin gene, resulting in proteins with varying degrees of strength.

Another team, led by Ervin H. Epstein at the University of California, San Francisco, found a similar type of keratin mutation in one family with 10 EB simplex patients. These researchers, whose report has been accepted for publication in SCIENCE, also found that the mutant keratin failed to form helical filaments.

A third research group, directed by Jouni Uitto of Thomas Jefferson University in Philadelphia, found that 20 members of a Finnish family affected by dominant dystrophic EB bore defective genes for collagen. In the October AMERICAN JOURNAL OF HUMAN GENETICS, they report that all 20 patients had blistering lesions where the skin's outer, epidermal layer had separated from the inner, dermal layer. Because collagen makes up the fibrils that anchor the two skin layers together, Uitto's team concludes that dominant dystrophic EB results from the collagen mutation.

Robert A. Briggaman, a dermatologist at the University of North Carolina in Chapel Hill, calls the three reports "absolutely essential" to finding a cure for EB, although he concedes that the search will be tough. Gene therapy may hold promise, but there's a catch, he says. Fuchs' group found that even tiny amounts of mutant keratin can block the normal protein's assembly into healthy filaments – which means that physicians would need to inactivate a patient's mutant gene as well as insert a healthy gene.

– C. Ezzell

Gene data place home of 'Eve' in Africa

A study of random genetic changes in one type of human DNA supports and expands a controversial 1987 DNA investigation that placed the origin of anatomically modern humans in Africa approximately 200,000 years ago. Although both studies indicate that modern *Homo sapiens* spread from Africa to other regions and replaced the descendants of an earlier African migration by *H. erectus*, some anthropologists still contend that modern humans originated closer to 1 million years ago in several parts of the world, with some genetic input from Neandertals along the way (SN: 6/8/91, p.360).

In the new work, molecular biologist Linda Vigilant of Pennsylvania State University in University Park and her colleagues studied mitochondrial DNA – located outside the cell nucleus and inherited only from the mother – obtained from 121 native Africans, 20 Papua New Guineans, one native Australian, 15 Europeans, 24 Asians and eight Americans of African descent. In samples from each individual, the researchers identified the chemical arrangement and random changes, or mutations, at the most rapidly evolving segment of mitochondrial DNA. The investigators assume that such mutations arise at a relatively constant rate, so that populations displaying greater numbers of such alterations represent older genetic lineages.

Native Africans possess more mitochondrial mutations than the other groups, the team reports in the Sept. 27 SCIENCE. Within each human population, specific chemical sequences turn up and others do not, but U.S. blacks show close mitochondrial DNA links to native Africans, the scientists assert.

Estimates of mutation rates in mitochondrial DNA provoke much controversy. Some researchers doubt the existence of any such "mitochondrial clock." But Vigilant and her co-workers argue that their analysis, based on a mutation rate derived from a comparison of mitochondrial DNA from humans and chimpanzees, indicates that the ancestral mother or mothers of modern *H. sapiens* lived in Africa between 166,000 and 249,000 years ago.

They made this calculation with two key pieces of information: a new reckoning that the chemical sequence of the rapidly evolving mitochondrial DNA in humans differs from that in chimps by nearly 70 percent, and a previous estimate that the chimp and human mitochondrial lineages split between 4 million and 6 million years ago.

The researchers note that even if the chimp-human split occurred 9 million years ago, as some scientists argue, human mitochondrial origins would extend back only about 373,000 years.

Such age estimates remain preliminary, they add. Possible differences in the mitochondrial mutation rates of humans and chimps may throw off the timing of the proposed mitochondrial clock.

Still, they conclude that the new data provide the strongest support yet for assigning a relatively young evolutionary age to the anthropological "Eve" – our common mitochondrial DNA ancestor in Africa.

– B. Bower

Science Service, Inc. is collaborating with JSTOR to digitize, preserve, and extend access to *Science News*. www.jstor.org