Duchenne marker: Cutting the odds

Ornithine transcarbamylase (OTC) deficiency and Duchenne muscular dystrophy have something in common besides lengthy names — they can both kill their victims. The sufferer of OTC deficiency lacks an important enzyme and is unable to properly break down protein, a condition leading to severe vomiting, coma and sometimes death (SN: 3/15/80, p. 166). Victims of Duchenne muscular dystrophy, the most common and deadly of all the muscle-degenerating diseases, seldom live beyond early adulthood (SN: 1/15/83, p. 42).

Both disorders are inherited, almost exclusively strike males and are caused by a similar defect — a deleterious gene on the X chromosome. Yet, while scientists have found and clearly identified the culprit gene for OTC deficiency, the precise location of the Duchenne gene has been a mystery. Now a team of geneticists at the Yale University School of Medicine in New Haven, Conn., has moved a step closer to that goal. In the Nov. 9 SCIENCE, the researchers report that by using a specific DNA probe, they have found that the OTC gene lies near where the Duchenne muscular dystrophy gene is believed to be.

The OTC probe consists of complementary DNA, and when it confronts the OTC gene DNA, it matches up rung for rung, like two halves of a symmetrically split ladder being glued back together. The OTC and Duchenne genes may be close enough for an OTC gene probe to detect Duchenne in fetal cells, says Uta Francke, one of the Yale scientists. It could be used to determine if a fetus has the same stretch of DNA as a close relative with Duchenne, but it would be accurate only about 80 percent of the time. The reason, she says, is because genes often undergo "recombination" when they pass from parent to offspring, and may not be inherited intact. As a result, until the actual Duchenne gene is found, "there are bound to be a number of false positives and false negatives." The probe is already being used in prenatal and carrier detection of OTC deficiency but not yet in predicting Duchenne.

According to Francke, the 80 percent accuracy rate is an improvement over the 50 percent "blind" prediction based on the laws of genetics. The pattern of inheritance of X-linked genes is often called crisscross inheritance. A male's X chromosome is transmitted only to his daughters, not his sons. The allele, or specific form of the gene, on the X in the daughter may then be passed to her sons, the chance of any son receiving either of his mother's alleles being 50 percent.

Francke says although researchers don't know exactly where the Duchenne gene is located, they have designated an area on the short arm of the X chromosome based on observations of several females who have had translocations — exchanges of genetic material — and have the disease. (This has not been seen with males.) "We assume that the break on the short arm of the X chromosome, where the piece is broken off as part of the translocation, must be at or very near the Duchenne gene because the gene has gotten disrupted and the girl has Duchenne," she says. There are about 12 such girls known worldwide, she says, and they all have an X chromosome translocation not seen in their mothers. Their other X is structurally normal, and apparently becomes inactivated — a normal cellular occurrence affecting only one X chromosome in females. However, the X chromosome that has lost some genetic material is still active. The transfers have destroyed the normal gene, she says, and the only gene remaining is the Duchenne. "The evidence is pretty strong," Francke says, "that there was a sequence that gives her Duchenne when it's changed, and it's located [near] the OTC gene."

Leon Rosenberg, another member of the Yale team, says the X chromosome mapping work should eventually prove valuable in revealing how X chromosome inactivation works, and also how other genes on the chromosome function.

"In the next year or two we'll have even better markers, ones closer to the Duchenne gene," predicts Robert Nussbaum of the University of Pennsylvania School of Medicine in Philadelphia. "Then the next step is the gene itself," he says. "We may not be that far away."

—*S.I. Benowitz*

Early reptile (?) makes first impressions

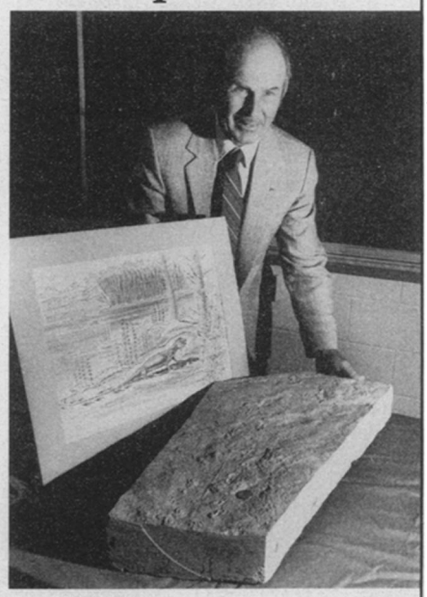
Roy Hines, a stone quarry operator in McCreary County, Kentucky, was ready to cut a slab of sandstone in late 1972 when something caught his eye. He noticed a 20-inch-long series of animal tracks on the stone and, out of curiosity, showed them to geologists at the U.S. Geological Survey.

The trackway was eventually sent to paleontologists Donald Baird of Princeton University in Princeton, N.J., and Nicholas Hotton III of the National Museum of Natural History in Washington, D.C., who now conclude that the footprints were made by either the earliest known reptile or an animal that represented a transition between amphibians and reptiles.

Hotton says that the tracks, dated at 310 million years old, are probably those of a reptile. "But without fossil remains," he adds, "I'm leery about saying it's definitely a reptile."

A trackway of more than 15 footprints in sequence, however, gives scientists a leg up on reconstructing the ancient creature. It was 12 to 15 inches long and looked somewhat like a modern iguana, although it was biologically different, explains Donald R. Chesnut Jr. of the Kentucky Geological Survey in Lexington, who participated in the analysis. The animal had a stride of 3½ inches and large feet with five digits each. A straight tail-drag mark among the tracks suggests that the tail did not swing or aid the animal in walking. The impressions were made in the soft, wet sediment of what was once a coastal lowland near a river, says Chesnut. While the animal probably ate insects and small amphibians, it is not known whether it fed on land or in water.

The earliest skeletal remains of a reptile are dated at 305 million years old, Chesnut notes. That specimen and the trackway animal are most likely part of the "stem-reptilian" family Romeriidae, from which all modern reptiles evolved, he says.



U. of Kentucky

Roy Hines displays sandstone containing a 310 million-year-old set of tracks. Artist's sketch shows a reptile that might have made the imprints.

Although the sandstone itself could not be dated, the scientists determined the age of the trackway by examining plant and spore fossils from a coal bed just above Hines' quarry. "We went back to the site three or four times, but couldn't find any other tracks or remains," says Chesnut.

Scientific work on the trackway was slow to get started, says Hotton, because it did not appear to be a promising find at first. The stone has no claw marks, which are sure signs of a reptile. Analysis did not move into high gear until several years ago, after the stone had been dated.

—*B. Bower*