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MOUSE MODEL REVEALS GENETIC BASIS FOR HIRSCHSPRUNG'S DISEASE

DALLAS — March 21, 1995 — Scientific advancement often involves an element of serendipity.

Dr. Masashi Yanagisawa's research goal was to understand the role of a hormone called endothelin in regulating blood pressure. Along the way, the associate professor of molecular genetics and investigator in the Howard Hughes Medical Institute at UT Southwestern Medical Center at Dallas discovered the genetic basis of a congenital intestinal disorder called Hirschsprung's disease.

Yanagisawa is credited with the discovery of endothelin, a potent hormone secreted by the cells that form the thin, inner lining of blood vessels. The researcher and his UT Southwestern colleagues set out to produce a mouse model that lacked the genes for the endothelin-B receptor and for endothelin-3, the protein product that binds with that receptor. They already had cloned fragments of the genes, so they were able to breed a line of mice with those genes knocked out.

The mice all were born with Hirschsprung's disease.

Named for the Danish physician who first described the disorder, Hirschsprung's disease — also known as megacolon — affects one in 5,000 babies. Some of the nerve cells that signal the colon to rid itself of fecal waste are missing. This causes a section of intestine next to the diseased portion to balloon out to five to 10 times its normal size. Without surgery, the infant soon dies.

Hirschsprung's disease has long been an enigma to medical science, since it is present at birth yet nine out of 10 cases have no family history of the disease. Now Yanagisawa believes that, although not familial, Hirschsprung's disease is definitely genetic.

"We knocked out the endothelin genes in mice and discovered human disease genes," the

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researcher said. "Our goal was to understand the role of the endothelins in cardiovascular regulation. We didn't expect the endothelin genes to be the genes for Hirschsprung's disease. We were just lucky that these two genes happened to be defective in mice with well-known and established recessive mutations that have been studied for many years, mouse piebald gene and lethal spotting gene."

Yanagisawa and colleagues reported on their discovery of the links between mutations in the endothelin-B receptor gene, the endothelin-3 gene and Hirschsprung's disease in two related papers in a recent issue of Cell. A third paper in the same issue by Yanagisawa and collaborators at Case Western Reserve University School of Medicine describes the human endothelin-B receptor mutation in a large family. The endothelin research was featured on the cover of the international journal.

Co-authors on the papers from UT Southwestern were Dr. Robert E. Hammer, associate professor of biochemistry and senior associate in UT Southwestern's Howard Hughes Medical Institute; Dr. James Richardson, associate professor of pathology; Howard Hughes associates Dr. Kiminori Hosada and Dr. Noriaki Emoto; and Amy Greenstein Baynash, Howard Hughes research technician.

"These papers describe the primary genetic defect that causes Hirschsprung's disease — in mice and man," Yanagisawa said. "Knowing that is a necessary first step. Without knowing the fundamental genetic defect, it is impossible to devise a fundamental cure.

"This research could lead to accurate diagnosis in embryo as well as diagnosis of carriers; of longer-range potential benefit, it could lead to effective nonsurgical treatment," he said.

Yanagisawa plans to collaborate with Dr. Luis Parada, director of UT Southwestern's Center for Developmental Biology, to explore the implications of his discovery in neural development. "Since Hirschsprung's disease is caused by a lack of neurons in the diseased

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portion of the colon, neurons that normally migrate from the neural crest down the intestinal tract during late embryonic development, we can now say that both endothelin-3 and the endothelin-B receptor are important for the survival or development or migration of neurons," Yanagisawa said.

Meanwhile he continues along his original research path: investigating the role of the endothelins in regulation of the cardiovascular system. He hopes to develop a line of mice that produce extra endothelin-B receptors in their intestines but still lack endothelin-B receptors in their blood vessels, to see if that will protect them from Hirschsprung's disease. Such a mouse would be an excellent model for cardiovascular research, Yanagisawa said. "The cardiovascular system seems to be subtly but significantly different in different animals, so you have to have the right model," he said, "and this mouse represents a very accurate analogue of human disease. The mouse has been thought to be too small for cardiovascular research, but it may be easier to miniaturize the technology than to try to adapt genetic research to larger animals."

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