Gutsy Genetics

Hunting down a gene for a children's digestive disorder

By KATHY A. FACKELMANN

Even before leaving the maternity ward, Linda C. Bendzewicz thought something wasn't quite right with her newborn. In the weeks that followed, she blamed her baby's fussy eating habits on a bad case of colic. Bendzewicz never dreamed that Hirschsprung's disease — the little-known digestive disorder that she herself had conquered as a child — had struck again.

At the time of her daughter's birth, scientists didn't really think of Hirschsprung's disease as a classic genetic disorder, in which a person inherits a bad gene and gets the disease. But now, 11 years later, research findings demonstrate that in some families at least, a single gene probably does cause this debilitating illness.

Two independent groups of researchers say they've homed in on the location of a gene thought to cause Hirschsprung's disease. The faulty gene appears along a stretch of chromosome 10, one of the 46 chromosomes that contain the genetic blueprint needed to make an entire human being. Each chromosome is made up of strands of DNA.

The reports of a single Hirschsprung's gene will force geneticists to reexamine the traditional view of this disease as one requiring the interaction of numerous genes, says Eberhard Passarge of the Institute for Human Genetics in Essen, Germany. Passarge wrote a commentary accompanying the two research reports in the August NATURE GENETICS.

Scientists believed that it took a multitude of factors, including genetic influences, to trigger Hirschsprung's disease. Thus, people with the disorder didn't necessarily think they could pass it on to their children. The new research suggests, however, that a single gene bears responsibility for some cases of this disorder. Passarge calls this finding "quite remarkable."

The new research also provides tantalizing clues to the origins of Hirschsprung's disease, which arises very early during development of the embryo in the womb.

The disease afflicts about one out of every 5,000 babies born in the United States. It takes its name from Danish physician Harald Hirschsprung, who described the condition in 1886 after caring for two young boys who suffered severe constipation and abdominal swelling, two hallmarks of the condition.

Kids with Hirschsprung's disease lack nerve cells in the smooth-muscle walls of the colon, which is part of the large intestine. The absence of these nerve cells interferes with peristalsis, the waves of muscular contractions that move stool through the intestinal tract.

Babies born with the genetic disorder may have trouble passing meconium, the thick, sticky material that is a newborn's first bowel movement. In other cases, infants appear healthy for several months but become very ill after they start to eat solid foods, which are harder to digest.

As waste material backs up, the colon above the blocked area becomes enlarged. Children usually pass small, watery stools and develop vomiting and bouts of diarrhea that alternate with constipation. A lackluster appetite can lead to a failure to grow properly.

Prior to 1948, almost all children born with Hirschsprung's disease died. Today, however, surgeons can remove the affected segment of the colon and sew the healthy ends together. Most children who undergo such surgery end up with nearly normal bowel movements, yet the surgery itself can be risky.

The tale of this particular gene hunt begins with a research team led by Giovanni Romeo at the Gaslini Institute in Genoa, Italy. These researchers had been treating a child with Hirschsprung's disease. In a routine genetic analysis, they noticed a large deletion — a loss of a segment of genetic material — in the child's chromosome 10.

To locate the deletion, the team constructed what's known as a physical map of the chromosome. Like a road map showing the distances between towns, a physical map of a chromosome shows the actual distances between genes on a chromosome.

Romeo and his co-workers wondered whether other people with this gut condition would show the same defect in the same chromosome. To answer that question, they teamed up with other researchers to study 15 families in France, Finland, and Italy. Each family had several members with Hirschsprung's. The researchers drew blood from family members and used DNA probes to search for distinctive "markers," or landmarks, along chromosome 10. Their search paid off when they noticed a telltale pattern of DNA that seemed to distinguish people with Hirschsprung's from their healthy relatives. The researchers believe the faulty gene lies within that DNA strip, which is near the middle of chromosome 10.

The group's discovery of the gene on chromosome 10 certainly would have generated considerable interest on its own. However, another team, this one led by Aravinda Chakravarti at the University of Pittsburgh, had undertaken the same hunt around the same time, with remarkably similar results. In a study of five large families from the United States and Australia, Chakravarti's group narrowed its search to the very same region of chromosome 10, strengthening the likelihood that a Hirschsprung's gene does exist there.

For scientists, the new finding offers the promise of a better understanding of Hirschsprung's disease and its origins. To learn more about this puzzling disorder, one has to look back to the womb — to the 5th through the 12th week of gestation.

During this time, certain cells located in what will be the baby's spinal cord

must migrate to the colon to ensure a healthy gut at birth. If those cells, called neural-crest cells, fail to start toward their destination or get waylaid, the result is a portion of the colon lacking crucial nerve cells.

No one knows what derails these cells in their journey through the embryo, but the new findings do offer some clues. "We're just beginning to understand what exactly regulates this migration," Passarge says.

Genes control the intricate dance of development that allows an undifferentiated blob of cells to become an embryo and then a fetus, eventually with fully developed organs. Both Romeo and Chakravarti speculate that Hirschsprung's disease occurs when a mutant gene disrupts the normal development of the intestines. Perhaps the normal version of this gene gives neural-crest cells the signal to begin their crucial journey to the wall of the colon, the investigators speculate.

However, not every family with a history of Hirschsprung's disease carries the newly implicated gene. "It is likely that there are going to be other genes on other chromosomes," Romeo says. Perhaps three or four genes will ultimately prove capable of causing the disorder, he adds.

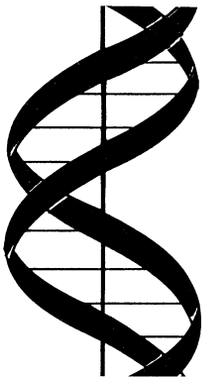
The Pittsburgh team is now studying a large Mennonite family with Hirschsprung's disease. That family, says Chakravarti, almost certainly has passed on a different disease-causing gene — one on a chromosome other than 10.

As for the gene on chromosome 10, both teams are racing to pinpoint its exact location and to identify the specific base pairs of nucleotides that make up its DNA. How long will those searches take? "We don't know," admits Chakravarti. "It could take a couple of years," or it could take significantly longer.

The importance of the new work may go beyond Hirschsprung's disease. The gene hunt may yield clues to other diseases caused by abnormal migration of neural-crest cells, Passarge says.

One such disorder is Waardenburg's syndrome, a pigmentation and hearing disorder linked to mutations in the *HuP2* gene (SN: 5/2/92, p.296). Waardenburg's syndrome arises when certain pigment-forming cells in the embryo fail to migrate from the neural crest to the eyes, hair, skin, or ears. Some people with Hirschsprung's disease also have Waardenburg's syndrome, notes Passarge. He wonders whether both disorders spring from a common precursor cell in the neural crest, a cell that somehow fails to reach its destination in the body.

The new research will leave a lasting legacy in the form of faster treatment for babies born with Hirschsprung's disease.



For families with a history of Hirschsprung's disease, the news about chromosome 10 provokes some worry but mostly relief. People who didn't realize the extent of their own risk may be concerned about having a child with the disease. On the other hand, the new findings may eventually lead to earlier diagnosis and better treatment for those who inherit this disorder.

In the past, people who had suffered from Hirschsprung's were not regarded as having a high risk of passing the disorder to their children, since doctors viewed the disease as requiring a large number of interacting genes and other factors. Family trees appeared to back that up: The inheritance didn't fit the standard Mendelian pattern of autosomal dominance, in which one gene dominates its "recessive" partner to cause disease, Chakravarti notes.

In recent years, however, geneticists have begun to suspect that Hirschsprung's disease follows a pattern called autosomal dominance with incomplete penetrance. That's a fancy term for a simple concept: Some people get a copy of the gene and show no clinical signs of disease; others inherit one copy of this gene and get symptoms. Researchers don't know why some people show signs of the disorder and others don't.

The evidence of a single-gene cause now suggests that for certain people, the chances of passing along Hirschsprung's disease are much greater than previously thought.

On a more encouraging note, the new research paves the way for the development of a blood test for Hirschsprung's disease. A baby born into a family with a history of this disorder could get a diagnosis at birth and could receive treatment before a life-threatening crisis develops.

With improved prospects for early detection, "families are really hopeful," says Bendzewicz, who cofounded the American Hirschsprung's Disease Association after her daughter was diagnosed with the disease. Her group recently merged with another support group to form the American Pseudo-Obstruction and Hirschsprung's Disease Society, Inc., based in Medford, Mass.

Right now, diagnosis can be tricky. Doctors can't always tell whether a child has mild digestive problems or something more serious, such as Hirschsprung's disease, says William Sieber, a retired pediatric surgeon who practiced at the University of Pittsburgh and who coauthored the new report with Chakravarti. In order to diagnose Hirschsprung's disease, they must obtain a snip of bowel tissue. Even then, doctors can easily miss the affected tissue, because the lack of nerves can occur anywhere along the coiled colon.

Sometimes physicians don't even suspect Hirschsprung's disease and parents don't recall anyone in the family ever having the disease. With diagnosis delayed, the child's colon becomes more and more blocked and can even become infected, Sieber says. Often, the result is emergency surgery.

That's what happened to Bendzewicz's nephew, Ryan, who is now 17. Ryan's condition went undetected until his appendix ruptured when he was 9 months old. Surgeons removed the appendix, but they didn't realize that Hirschsprung's disease was the underlying problem until Ryan continued to have digestive problems after the operation.

Bendzewicz went through a similar delay with her daughter, whose colicky episodes remained undiagnosed until she stopped growing at 5 months of age.

Some children actually die before anyone figures out what's wrong with them. "My daughter and nephew were fortunate to survive complications from not being diagnosed at birth," Bendzewicz says.

With a fast and simple blood test for all the genes involved, parents would know right away whether their baby inherited a gene for Hirschsprung's disease, Sieber points out. Without delay, physicians could begin the tests that confirm the absence of colon nerve cells. Surgeons could operate soon after birth — a practice that avoids life-threatening complications and often leads to a better outcome, Sieber says.

While finding the locations of genes won't prevent Hirschsprung's disease, Bendzewicz believes such work will leave a lasting legacy in the form of faster treatment for babies born with the condition.

"The earliest possible diagnosis gives these babies a much healthier start in life," she says, "and it certainly brings more peace of mind for their parents." □