Chew on This: Mutation May Be Responsible for Tooth Loss, Colon Cancer

A decade ago, scientists sometimes explained the ABCs of genetics with the simple rule that each gene has one function. Today, this nice, neat and, as some would say, naive concept appears to have fallen largely out of favor. In its place, researchers have fashioned the concept in which a gene typically has multiple functions and/or physiologic effects, sometimes in seemingly unrelated parts of the body.

Just how seemingly unrelated can these manifestations be? Recently, a team of Finnish scientists reported discovering a large family that is predisposed to both colon cancer and a rare congenital dental malformation. They say the cause is a specific mutation in a gene called AXIN2, which is selectively expressed in certain types of organ development and also has a regulatory role in cell homeostasis. In essence, the mutation seems to disrupt tooth development early in life and later contributes to the emergence of polyps and eventually colon cancer.

According to the scientists, their data mark one of the few known instances in which a gene mutation causes a hypoplasia in one organ and a hyperplasia in another. Moreover, if their follow-up studies confirm and/or strengthen their existing data, they say dentists may at the very least need to remain aware of the possible association, an example of how molecular genetic discoveries today increasingly cross traditional disciplines.

All in the Family

Tooth agenesis—the lack of one or more permanent teeth—is the most common congenital malformation in humans. It comes in two main subtypes, one of which is the more severe oligodontia. Although the disease is fairly rare, people with oligodontia do not produce six or more permanent teeth, and these conditions are often associated with other malformations of the nails, hair, and other ectodermal-derived tissues.

Given the importance of proper tooth formation across species, a team of researchers at the University of Helsinki has long been interested in identifying genes that might play a role in oligodontia. That led them a few years ago to a four-generation family, in which about half of the family members lacked at least eight permanent teeth, primarily permanent molars, premolars, and various incisors.

After narrowing the location of the altered gene to a specific region of chromosome 17, the scientists noticed something intriguing. Among the candidate genes in this region was AXIN2, whose protein product aligns itself within the wnt signaling pathway. This intensely studied pathway plays a key role in early organ differentiation and development. It also serves a key regulatory role in several basic cell functions, including proliferation. In fact, it had been reported a few years earlier that mutations in AXIN2 may be associated with colorectal cancer in people.

“We were immediately interested in AXIN2, because we knew that one of the family members also had colorectal cancer,” said Pekka Nieminen, M.Sc., an author on the paper and a scientist...
at the University of Helsinki. “Then we looked at AXIN2 in this person and found a mutation. We knew from the literature that many others in the family would be in danger of having colorectal cancer. So we sent them for a colorectal exam, and that’s how we made the link.”

The link was that eight of the 12 family members with oligodontia either had colon cancer or precancerous polyps. All available family members without the dental condition had no signs of colon cancer. “In this family, the oligodontia was quite severe,” said Nieminen. “Right now, we think that the predisposition to cancer applies only to those who have the most severe types of tooth agenesis, even then only a minority of them. I say this because I don’t want people with mild forms of tooth agenesis to worry.

“But, for those with the most severe forms of tooth agenesis, only a very small fraction of the mutations are known,” added Nieminen. “It’s possible that new findings will come that connect tooth agenesis to cancer, but at this point, it seems not to be a very common phenomenon.”

**Molecular Logic**

Despite this seemingly odd clinical coupling of teeth and colon cancer, Nieminen and others say the finding bears a certain molecular logic. “In developmental biology, it’s well known that the same signaling pathways that regulate the development of given organs, including teeth, can cause cancer if they go wrong,” said Nieminen. “So, in that sense, this is not so curious. But, to our knowledge, this is one of the first cases in which there is a hypoplastic malformation that is caused by the same mutation that causes cancer.” Their study was published in June in the *American Journal of Human Genetics*.

Kenneth Weiss, Ph.D., who studies the evolution of complex traits at Pennsylvania State University in University Park, said he wonders whether another interpretation might be valid. “Many of these genes, including wnts, are used in so many tissues that it doesn’t seem that strange that a gene would be thought of to inhibit something in one context but to activate it in another,” he said. “I would not characterize this as hypoplasia and hyperplasia. Signaling factors can trigger a variety of responses, including differentiation of a cell, apoptosis, growth, etc.—all of which mean change in gene expression.

“He however, I think a more subtle issue is that the dental results are not inactivating results, but ones that alter a patterning process in a quantitative way,” Weiss continued. “Similarly, in
colonic crypts are stem cells, and altered growth, division, differentiation, or other similar phenomena of those cells could appear after decades to have ‘activated’ something, when that is not an accurate description of what the mutations do. I would not call this a loss-of-function mutation, but an ‘alteration of function’ mutation.”

Nieminen said he and his colleagues continue to follow up on AXIN2 and its role in oligodontia. They also are working closely with cancer biologists to further pin down the possible association with colon cancer and determine if the cancer phenotype might involve other organs.

—Robert Longtin