Shared Mutation for Two Childhood Diseases

By Cathryn M. Delude

The rare genetic disease fibrodysplasia ossificans progressiva (FOP) turns a child’s muscle tissue into bone, forming a second skeleton that is eventually fatal. Frederick Kaplan, M.D., a leading FOP researcher at the University of Pennsylvania’s Perelman School of Medicine, helped identify the mutation responsible and searched for inhibitors. Eight years later, he learned about a bizarre coincidence: Four research teams independently found the same mutation in a rare, inoperable, and incurable pediatric brainstem tumor called diffuse intrinsic pontine glioma (DIPG).

The mutated gene, ACVR1 (also called ALK2), has no previous association with cancer. Researchers found this gene in almost 25% of DIPGs but in no other brain tumors. Despite having the mutation in every cell, FOP patients do not get DIPG.

ACVR1 encodes a cell surface receptor for bone morphogenetic proteins (BMPs).

“We were especially excited because that’s a druggable target, and we can benefit from the work on an inhibitor [LDN-193189] already under way in the FOP field,” said Chris Jones, Ph.D., a DIPG researcher at the Institute of Cancer Research in London, who led one of four studies in Nature Genetics (Nat. Genet. 2014;46:457–61).

“All of a sudden, we have an explosion of insight that occurs when the cancer world and the developmental world meet,” Kaplan said. “There’s nothing worse than horrible diseases that affect children, and here are two horrible childhood diseases linked by a connection to the same mutation. We now have the best scientists in the pediatric cancer field consulting with scientists in the FOP field to gain insights into mechanisms and treatments that will help children with both diseases.”

Blackest of Black Holes

Each year, about 200–300 U.S. children with a median age of 6–7 years are diagnosed with DIPG. DIPGs belong to a group of pediatric high-grade gliomas (HGGs) that look identical to glioblastoma. Traditionally, biopsies are not performed, since results would not change therapy, which for lack of better understanding is based on adult gliomas. Of all the dismal pediatric outcomes for HGGs, DIPGs have the most devastating.

“Median survival for the kids is 9 months. Everyone is dead within 2 years,” said Mark Kieran, M.D., Ph.D., of Boston’s Dana–Farber Cancer Institute, a coinvestigator of one of the studies (Nat. Genet. 2014;46:451–6). “We’ve made no progress in those tumors because we literally knew nothing about them.”

“It wasn’t clear whether DIPGs have such devastating outcomes because they cannot be removed surgically from the brainstem, or because they have a distinct biology,” said Suzanne Baker, Ph.D., who led a study conducted by St. Jude Children’s Research Hospital–Washington University Pediatric Cancer Genome Project in Memphis, Tenn. (Nat. Genet. 2014;46:444–50).

The four new studies jointly analyzed almost 200 DIPG tumors, using both autopsy and newly available biopsy tissues. Two studies also analyzed other pediatric HGGs. Except for ACVR1 and several other genes involved in developmental pathways or epigenetic regulation, even advanced tumors had few other known brain cancer genes such as BRAF or IDH1 or -2.

“This may mean that very few mutations are needed to initiate and drive the cancer,” said Cynthia Hawkins, M.D., Ph.D., who led the study from the Hospital for Sick Kids in Toronto (Nat. Genet. 2014;46:451–6).

“It’s an outstanding example of team science addressing a critical limitation in our knowledge of childhood malignant brain tumors,” said neurooncologist John Kuttesch, M.D., Ph.D., chief of pediatric oncology at the University of New Mexico. “The investigators have now identified the genetic background that contributes to the development of DIPG and other midline HGGs in children. Now we have the opportunity to think about targeting those genes.”

Weakly Activating ACVR1 Mutation

FOP researchers had learned that when BMPs bind to the receptor that ACVR1 encodes, they activate a pathway that ultimately affects cells in different locations and stages of development. The DIPG
studies show that the mutation derived from the DIPG cells also aberrantly activates downstream genes in the BMP pathway. However, Baker’s group found that expressing the mutation in mouse models did not independently cause cancer.

“ACVR1 mutation only mildly activates the BMP pathway,” so how it leads to cancer isn’t clear, said Adam Resnick, Ph.D., a researcher at the Children’s Hospital of Philadelphia not involved in these studies. “It doesn’t work like a classical oncogene.”

“We think the ACVR1 mutation needs a partner in crime,” said Nada Jabado, M.D., Ph.D., a coinvestigator on Kieran’s study at McGill University in Montreal. A key partner may be a histone protein mutation that she, Baker, and Hawkins independently identified in 2012 in pediatric, but not adult, gliomas (in Nature 2012;482:226–31, Nat. Genet. 2012;44:251–3), and Acta Neuropathol. 2012;124:439–47, respectively). Histone proteins package DNA in tight spools of chromatin, with a “tail” that helps determine whether genes should be accessible by activating transcription factors. The effects are epigenetic because they modify gene activity without changing DNA.

An Epigenetic Partner
In that previous work, researchers identified a new mutation in histone protein H3, called p.Lys27Met, or K27→M. Methionine replaces lysine at position 27 in the protein. Adding nuance, two H3 mutations, H3.1 and H3.3, cause the same substitution, but H3.3 occurred mostly in the brainstem/DIPGs. The H3 discovery was unexpected, Baker said, and served as the first clue that DIPGs have a distinct biology.

The new studies found the H3 mutation in almost 90% of DIPGs and analyzed how the two variants associated with different mutations. The researchers identified H3.3 mutation in 60% of DIPGs. The less common H3.1 occurred almost exclusively in DIPG. After H3, the most common mutation in DIPG was ACVR1 (at almost 25%), which almost always occurred with the H3.1 variant.

“We don’t really know what’s happening at the K27→M substitution,” Jabado said. “We think it’s losing a repressive mark.”

That loss could make a cadre of genes accessible, possibly including ACVR1. Indeed, Hawkins found that expressing ACVR1 and the histone H3 mutation together had an additive effect on the downstream BMP pathway, suggesting cooperation.

Histone H3 is not yet targetable with drugs, but in these studies it often occurred with mutations that might be. In addition to ACVR1, those included PDGFRA (which was mutually exclusive to ACVR1 in DIPG), FGFR1 (in the thalamus), and NTRK (in 40% of infant HGGs outside the brainstem, which were less aggressive)—all genes involved in the developmental PI3K pathway, often dysregulated in cancer.

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Emerging Story
Now the cancer and FOP communities can only speculate about how the same ACVR1 mutation may connect both wildly different diseases. The working hypothesis is that in FOP, the germline mutation allows cells in muscle tissue to dedifferentiate and activate a different developmental pathway that tells the cells to redifferentiate as bone cells. “Dedifferentiation is also a hallmark of cancer, because it allows cells to reactivate a developmental program where they are allowed to divide again,” said Kieran. “In FOP, cells dedifferentiate so they can turn on a different fate program. In tumors, they dedifferentiate so they can turn on a different proliferative program.”

Thinking About Therapy
The research has immediate implications for an open and accruing DIPG trial led by Kieran at Dana–Farber that involves taking biopsies for research, which is incorporated into the Kieran–Jabado study. On the basis of the biopsy results, the researchers tailor participating children’s treatments with approved drugs and will add new drugs as they become available.

“After 40 years of frustration in empiric treatment approaches in DIPG,” Kuttesch said, “these reports offer a more rational approach in developing new therapies, and hope for the children and families affected by this devastating disease.” And, Kaplan added, “for those affected by FOP”

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