Scientists Find Genetic Changes Linked to Cancer in Children

Like a house with a faulty foundation, cells with genome instability are more prone to accumulating DNA changes.

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A new study has identified a group of genetic changes that are likely involved in the development of cancer in children. According to the findings, genomic changes affecting large pieces of DNA, called structural variants, contribute to an estimated 1% to 6% of pediatric solid tumors.

Structural variants occur when large chunks of the genome get deleted, added, duplicated, flipped around, or moved during cell division. The researchers focused on germline structural variants, meaning those that are present at birth and typically inherited from a parent.

To conduct the study, the team analyzed the genomes of more than 1,700 children with neuroblastoma, Ewing sarcoma, or osteosarcoma. They also looked at the genomes of the children's parents and of unrelated adults without cancer, for comparison.

The children with cancer had more structural variants that were predicted to change the function of a gene than the adults without cancer, they found. And boys were much more likely than girls to have structural variants that involved very large pieces of DNA.

Findings from the NCI-funded study were published January 3 in Science.

"From a research perspective, this [study] is really like planting [a] flag in the ground," said the study's co-leader, Ryan Collins, Ph.D., a computational biologist at Dana-Farber Cancer Institute. It "shows that this is a whole class of genetic variation that … plays a role in an individual's risk for getting cancer early in life, at least in the three diseases that we studied," Dr. Collins said.

The findings will help researchers better "understand the earliest biology that leads to these diseases," said the study's other co-leader, Riaz Gillani, M.D., a pediatric oncologist at Dana-Farber Cancer Institute.

And with that better understanding, hopefully scientists will find treatments that precisely target that biology, Dr. Gillani continued. Such targeted treatments would have several advantages over the current "sledgehammer approach" of chemotherapy and radiation used to treat most children with solid tumors, he added.

Genetic causes of pediatric cancer

Cancer is caused by damage to DNA that alters how cells function, especially how they grow and divide.

For adults, it's generally thought that cancer takes decades to develop as DNA damage builds up over time, mostly from exposure to carcinogens and natural errors that occur when cells divide.

But for children, who can develop cancer before their first birthday, it's an entirely different scenario. Children haven't lived long enough to accumulate lots of DNA damage from carcinogens and natural DNA errors, so many experts suspect that pediatric cancers are mostly caused by inherited genetic changes.

Inherited genetic changes are currently pinpointed as the cause of 8% to 10% of childhood cancers, similar to that observed in adult tumors.

But that estimate comes almost exclusively from studies of "small shifts and variations in the genome," such as single-letter switches in the DNA code, said Jaime Guidry Auvil, Ph.D., director of NCI's Office of Data Sharing. Dr. Guidry Auvil has led several childhood cancer genome projects but was not involved in the new study.

Structural variants, which affect 50 to upwards of a million DNA letters, have been harder to study due to technical limitations of traditional DNA sequencing technologies, Dr. Collins explained.

"Only recently have we started to really get a handle on how to detect these types of germline rearrangements in the human genome," he said.

Structural variants disrupt key genes

To identify germline structural variants that may raise the risk of pediatric cancer, the team compared the DNA of around 1,700 children with cancer, more than 900 parents of those children, and over 6,000 unrelated adults without cancer.

The average person has thousands of structural variants, Dr. Collins explained, and the researchers found more than 5,000 germline structural variants in every individual in the study.

But, compared with their parents and unrelated adults, the children had an average of 6 to 10 more structural variants that were predicted to change the function of a gene. In many cases, the structural variant lopped off a sizable chunk of a gene.

Only a small percentage of the variants affected known cancer genes or genes that cause hereditary cancers. For instance, a small group of structural variants among the children with Ewing sarcoma and neuroblastoma quashed the activity of known cancer genes that help repair broken DNA.

Other structural variants affected genes that are critical for the development of the organ or tissue where the cancer started. Neuroblastoma starts in nerve cells, for example, and several genes that are important for nerve cell development were affected by structural changes in children with neuroblastoma.

These findings highlight the importance of looking at structural variants on a large scale, Dr. Guidry Auvil said. “Happily, we have whole genome sequencing data from many childhood cancer projects to be able to do those analyses” including TARGET, the Gabriella Miller Kids First Pediatric Research Program, and the Childhood Cancer Data Initiative, she added.

Boys with cancer have more large structural variants

The researchers also focused in on large structural variants—those involving more than a million DNA letters. Large structural variants raise the risk of several developmental disorders, so the team reasoned that they may also have a role in pediatric cancer.

As they suspected, the children were more likely than the adults to have a large structural variant.

But they were surprised to find that this difference was entirely driven by the high frequency of structural variants in boys with cancer, who were much more likely to have large structural variants than the men without cancer.

Again, very few of those variants affected known cancer genes. Instead, they appeared to be randomly scattered throughout the genome.

That finding is both perplexing and enticing, Dr. Collins said, because it almost guarantees that “there probably are pediatric cancer–specific risk genes that we haven’t yet discovered.”

“We have to go deeper than the traditional investigation [of known cancer genes], especially in these tumors that are showing up in very young children,” Dr. Guidry Auvil agreed.

“We’ve got to look at all of the data with a little bit more of an open mind,” she added.

Overall, the researchers estimated that structural variants are involved in the development of 1% to 6% of neuroblastomas, Ewing sarcomas, and osteosarcomas. That is a rough estimate limited by the relatively small number of children in the study and the exclusion of certain types of structural variants due to technical limitations, the team noted.

No single cause of pediatric cancer

Germline genetic changes are those that are present at birth in every cell in the body. In the study, nearly all of the germline structural variants present in the DNA of children with cancer were inherited from a parent, the researchers found.

But because the parents of these children didn't have cancer, the finding suggests that there are likely additional factors at play, Dr. Collins explained.

There's a tendency to think "about the cause and the gene" for cancer, Dr. Gillani said, but it is rarely ever the result of a single cause.

An "obvious next step is to take the holistic composite view of everything that's in these kids' genomes," Dr. Collins added, meaning structural variants as well as small mutations and other genetic changes. "Follow-up studies are under way on that avenue," he said.

Dr. Guidry Auvil agreed, saying, "I think we're doing a disservice to cancer patients if we don't gather as much information as we can about what's going on in these small bodies and start to look at all of these findings collectively," including "when and where and how these [genetic] events happen" during children's development.

Understanding and targeting genome instability

The study results hint that children with neuroblastoma, Ewing sarcoma, and osteosarcoma may be prone to acquiring excessive genetic errors, a phenomenon known as genome instability, wrote Jayne Hehir-Kwa, Ph.D., of Princess Máxima Center for Pediatric Oncology in the Netherlands, and Geoff Macintyre, Ph.D., of the Spanish National Cancer Research Center in Spain, in an accompanying perspective.

Like a house with a faulty foundation, cells with genome instability are more prone to accumulating DNA changes, such as structural variants.

During childhood growth spurts, cells are rapidly growing and dividing, Drs. Hehir-Kwa and Macintyre added. If a child's cells are marked by genome instability, these growth spurts could open the door to acquiring a whole slew of new structural variants, they continued. And that would put those children at greater risk of developing cancer.

Previous studies of childhood cancers, which have found small mutations in genes that normally repair damaged DNA, have also provided evidence that genome instability may be at play.

The upside is that pediatric cancers may be able to be treated with available drugs that target genome instability, Drs. Hehir-Kwa and Macintyre noted. Certain drugs, like PARP inhibitors and platinum-based chemotherapy, work better against cancers that already have a lot of damaged DNA, they explained.

Overall, Drs. Collins and Gillani said, the findings point to a class of genetic changes that are not only driving some childhood cancers but may be targetable in the future.

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