Gene therapy technique may pose harm: study

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By Keith Mulvihill

NEW YORK (Reuters Health) - Scientists announced Thursday that their research into the a particular type of gene therapy raises important questions about the safety of using retroviruses to carry genes into people.

In gene therapy, a vector - usually but not always a virus -- is used to carry a healthy gene into the cells of patients. If it works correctly, the virus inserts its DNA and the new gene into cells and corrects the genetic defect.

Earlier this year the Food and Drug Administration halted certain gene therapy trials after two boys in France developed leukemia while they were taking part in a gene therapy trial that aimed to bolster bone marrow with genetically engineered immune cells. The treatment appeared to be working remarkably well in 10 of the group of 11 boys who had a hereditary disease that left them without an immune system.

The leukemia cases prompted researchers to speculate that the retroviral vector used in the trial may have been integrated near a known cancer-promoting gene.

In the current study, lead investigator Dr. Shawn M. Burgess and colleagues analyzed where in the human genome two types of retroviruses are likely to permanently integrate.

The researchers looked at one of the most commonly used retroviruses in gene therapy -- murine leukemia virus (MLV), a mouse virus that can infect human cells. And they also looked at another retrovirus -- HIV-1.

"MLV was used in the French study where two children, of 11, developed leukemia," said Burgess.

Burgess's team looked at 903 MLV and 379 HIV-1 integrations and found two different results for the two viruses. "This was unexpected," he said.

"HIV-1 likes to integrate anywhere in genes, and MLV likes to integrate around the beginning of genes where the important regulatory sequences are," he explained.

The main finding, according to Burgess, is that viruses integrate into sequences non-randomly and it appears that every virus will do this differently.

"Thus, nothing about the safety of a particular retroviral treatment can be assumed," he said.

In the past the assumption was that the integrations were random and that the risk was low that the virus would integrate somewhere risky in the DNA code, noted Burgess, who is with the National Human Genome Research Institute in Bethesda, Maryland.

"This is apparently not true," he said.

What's more, the findings seem to jibe with what happened in the two children who developed leukemia.

"The integrations that are believed to cause the problems both fit the favorite-site profile we determined for MLV," Burgess said.

"Thus, the risks must be higher than we originally thought," he added.

Burgess noted that the findings, which are published in the journal Science, are the first-ever documentation of a large number of integration sites for two viruses showing they behave very differently and there are inherent risks in using them for gene therapy.

As such, he recommends that "any new vector should be profiled to determine the integration biases of the vector to be used to help evaluate relative risk."

The new discovery may very well be a set-back for gene therapy, as there are few alternatives to using retroviruses as vectors, according to Burgess.

"None of (the other types) are as far along as the retroviral vectors," he said. "They all have their own problems that are even larger than the viruses."

"At the moment, (retroviral vectors) still seem the most promising, even with the associated risk," he added.

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