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Jumping genes: a marker for early cancer diagnosis? An interview with Dr Kazazian

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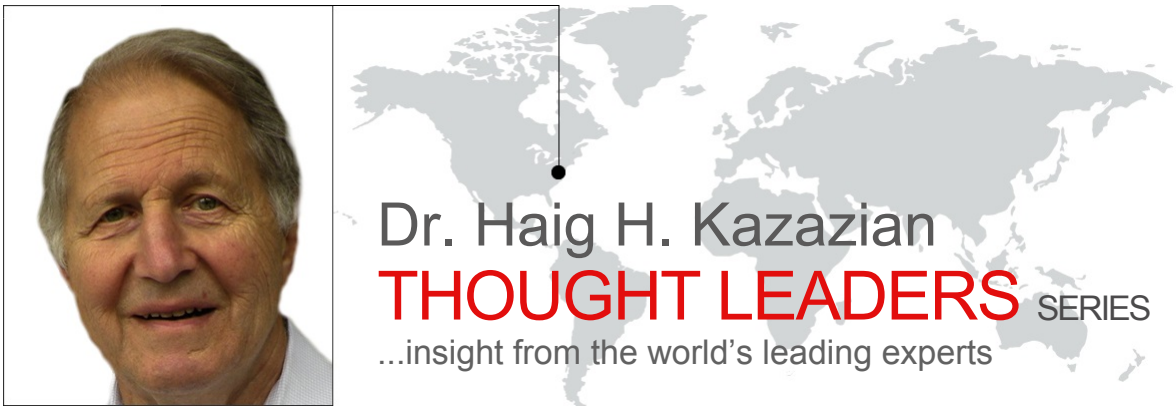
Interview conducted by James White, MPsych



What role does the LINE-1 "jumping gene" play in the human genome? Has it previously played a different role?

In the genome of every human being, there are about 80-100 active LINE-1s that are capable of mobilizing by a copy and paste mechanism to a new location in the genome.

Upon jumping to a new site, the LINE-1 might alter the function of nearby genes, or knock out a gene by jumping into its protein coding region.

We now know of over 100 examples of patients that acquired a disease because a LINE-1 jumped into one of their genes.

LINE-1s have also played roles in evolution, for example by likely providing the reverse transcriptase sequences for enzymes called telomerases that stabilize the ends of chromosomes.

Why are jumping gene copies so prevalent in the human genome?

These are very, very old sequences, probably older than 500 million years as they are found in certain yeast.

So over evolutionary time they have jumped in the genome and then those jumped copies have become inactivated by mutation so now we end up with over 500,000 copies of LINE-1s, mostly dead, that make up almost 20% of the human genome.

On top of those copies, the proteins of LINE-1 are also responsible for mobilizing other human jumping genes, so overall LINE-1 is responsible for over 1/3 of our genome.

What impact do the inactive jumping gene copies have for us?

The inactive copies have often been coopted to provide sequences that affect expression of nearby genes. They can provide new splice sites within genes, all kinds of functions can be newly acquired by inactive LINE-1 sequences.

In addition, two inactive LINE-1s of very similar sequences that are say 5 million base pairs apart in the genome can be mispaired and produce a deletion or a duplication of the sequences between those LINE-1 sequences.

Can you briefly describe how you highlight an active LINE-1 gene amongst so many other inactive LINE-1 copies?

You look for a LINE-1 sequence that is 6 kb in length because most of the inactive sequences have lost their front ends during jumping. Active elements need their front ends in order to be expressed.

Then you make sure that the sequences that encode the two LINE-1 proteins are still intact, and that they have other tell tales of human specific sequences. If these criteria are met, there is an excellent chance that the element

is active as determined in cultured cells.

How are jumping genes implicated in cancer development? Are they implicated in all types of cancer or just specific types?

We and others have found that there are somatic new insertions of jumping genes occurring in certain types of cancers, particularly those of epithelial (lining) cell origin, such as cancers of the GI tract.

We now believe that most of these LINE-1 insertions occur in normal cells of the GI tract with specific insertions in different proportions of cells, i.e., some insertions may be in 1 cell in 1 million and others may be in 1 cell in every 10.

Depending upon which normal cell becomes cancerous, the insertions present in that normal cell become clonal in the cancer. Other insertions may occur during cancer development.

Can you please describe how a LINE-1 insertion could disrupt the capability to fight cancer? And specifically how the insertion might cause a tumor to metastasize and progress?

A LINE-1 insertion might knock out the function of one copy of a gene that has a tumor suppressor function. However, another hit would be required in the second copy of the gene.

It would be unlikely to cause tumor progression without that second hit. So it would merely cause susceptibility to the cancer, but this is like any other mutation. For metastasis, the insertion could knock out a gene whose function is important to slow or prevent metastasis.

Do you think that LINE-1 genes are driving cancer development or are created as a side effect of cancer?

This is the 64,000 dollar question. I suspect that most insertions are merely passengers and not involved in cancer development. However, we do know of at least two instances where LINE-1 insertions are extremely likely to be causative of cancer development.

Thus, the big question is, Are LINE-1 insertions involved in 1 in 1000 cases of GI cancer or are they important in 1in 50 cases? If the latter, then they are quite important in etiology.

How will detection of extra, active LINE-1 genes affect the early detection of cancer? Could future patients be screened for new LINE-1 insertions?

LINE-1 insertions are stuck in the genome where they land. That is why we have so many in our genome.

If one could obtain a small piece of the cancer at surgery and find the LINE-1 insertions in the cancer that appear clonal, one could screen the patient periodically for the insertion in the blood. Upon finding the insertion in blood DNA, one could determine that the tumor had re-appeared.

What are the next steps in your research?

We want to determine whether we can find insertions in tumors in the blood later. Can we determine that these insertions can be used as biomarkers for the tumor?

We are also wondering whether these insertions can be used as therapeutic markers for the tumor if they are we could then attempt to kill all the tumor cells while killing 1 in 100,000 of the normal cells.

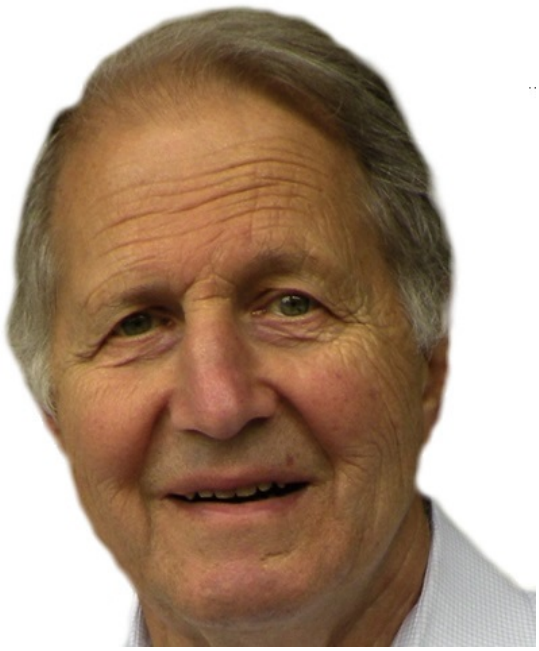
Also, we want to determine whether any of these insertions are important for the tumor phenotype. In tissue culture of cancer cells, we hope to remove the insertion and determine whether the phenotype revert back toward the normal state.

Where can readers find more information?

They can look at the three papers:

- Rodic et al. Nature Medicine.
- Ewing et al. Genome research.
- Doucet-O'Hare et al. PNAS that appeared in August, 2015.

About Dr Kazazian



Dr. Kazazian received his A.B. degree from Dartmouth College in 1959. He then attended Dartmouth Medical School, a two-year school at the time, and finished his M.D. degree at Johns Hopkins University School of Medicine.

At Hopkins, he met his wife of 52 years and married during his internship in Pediatrics at the University of Minnesota Hospital.

After two years training in Minneapolis, he returned to Johns Hopkins for a two-year fellowship in genetics with Barton Childs, M.D. He then trained for two and 1/2 years in molecular biology in the lab of Harvey Itano, M.D., at the NIH.

After a third year of pediatric training at Johns Hopkins, he joined the faculty there in 1969. He rose through the ranks to become a full professor in 1977, and at that time, he headed the Pediatric Genetics Unit. In 1988, he became Director of the Center for Medical Genetics at Johns Hopkins.

After 25 years on the Hopkins faculty, Dr. Kazazian was recruited to the University of Pennsylvania, School of Medicine as Chair of the Department of Genetics in 1994. At Penn, he recruited 10 young faculty to the department.

In 2006 he stepped down as department chair, but remained as the Seymour Gray Professor of Molecular Medicine in Genetics until 2010.

In July 2010, he returned to Johns Hopkins as a Professor in the Institute of Genetic Medicine. Dr. Kazazian is still actively involved in molecular genetic research, concentrating for the past 25 years on mammalian and human transposable elements, or "jumping genes".

Prior to 1988, he characterized much of the normal variation, dubbed "haplotypes", in the cluster of genes involved in production of the beta chain of human hemoglobin. With Stuart Orkin at Harvard, his work led to the essentially complete characterization of the mutations causing the ß-thalassemias, common anemias in regions of the world endemic for malaria.

Dr. Kazazian has published nearly 400 papers and a book entitled, "Mobile DNA: Finding Treasures in Junk." He is a member of a number of national organizations, including the Institute of Medicine of the National Academy of Sciences and the American Academy of Arts and Sciences. Dr. Kazazian also has received a number of honors for his research, most notably the 2008 William Allan Award, the top honor of the American Society of Human Genetics.