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Posted on Thu, Dec. 18, 2008

Beginning to crack the code of 'junk DNA'

By Faye Flam

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To scientists, it was a mystery. Most of the genetic material we carry in our cells seemed to have no purpose.

It seemed so useless, some called it "junk DNA."

Weirder still, geneticists noticed that some of the junk has a life of its own, copying itself, viruslike, and jumping around the DNA.

This phenomenon had never been documented in humans until geneticist Haig Kazazian started studying boys with the blood-clotting disorder hemophilia.

Over years of painstaking research, Kazazian, now at the University of Pennsylvania, found that these straying bits of DNA can land in important genes like so much molecular debris - leading to a few cases of hemophilia, muscular dystrophy, and several other genetic disorders.

For his lifetime of achievements, he was given one of the highest honors in his field last month: the Allen Award from the American Society of Human Genetics.

Kazazian, 71, has no plans to slow down. He is investigating whether this type of self-replicating junk DNA holds more power over human illness than has previously been imagined. It might influence our risk for cancer, neurodegenerative diseases, and other common conditions.

"The one thing that drew me to Haig is his intellectual curiosity and his fearlessness," said geneticist John Moran, who studied under Kazazian at Johns Hopkins University before becoming a professor at the University of Michigan. "He took the field in a new direction - he really was one of the pioneers."

Johns Hopkins genetics professor Aravinda Chakravarti said that while geneticists looked at mice or fruit flies in search of clues to human disease, Kazazian also worked the other way, starting by unraveling mysterious medical cases to better understand how human DNA works.

Oddly, humans appear to carry much more DNA than we need. If you stretched out the DNA in just one cell, it would extend six feet - spelling out a four-letter code three billion letters long.

In a vast sea

Only 1 or 2 percent of all that is made up of genes - sequences that spell out recipes for a host of biological molecules known as proteins.

These genes are embedded in all of this other DNA like islands in a vast sea.

About a third of the other 98 percent of our DNA is made of "introns" - stretches of code that are spliced out when it's time to transcribe the genes into proteins. The rest is the stuff formerly called junk.

If there are messages written there, they are not altogether accessible. If the coherent 2 percent read like Harry Potter, the so-called junk DNA could be the more opaque stretches of James Joyce's *Ulysses*.

Kazazian didn't set out initially to investigate any of this. When launching his genetics career in the 1960s, he wanted to work on combating inherited diseases, such as hemophilia, muscular dystrophy and thalassemia, a form of anemia.

In high school and college, he imagined that he would become a doctor. That was the profession his father said he would have followed had his family not been imprisoned in a Turkish concentration camp in 1915 - along with thousands of other Armenians living in Turkey.

New vistas

Kazazian's father was 14 at the time. Both of his parents, all of his siblings, and his grandmother died in Turkey. In the early 1920s, he came to the United States and became a rug merchant. Medicine would have to wait until the next generation.

But Kazazian switched from medicine to genetics in the 1960s, inspired by the new vistas of knowledge the field was opening up.

In 1969, he joined the faculty at Johns Hopkins, where he began studying genetic diseases. He and other geneticists at the time were finding that dozens of different errors in the same gene could lead to the same disease.

He expected something similar when he started studying hemophilia, which is caused by various defects in a gene called factor VIII, carried on the X chromosome.

People with hemophilia often suffer bleeding into their joints, Kazazian said. And even a simple dental visit can leave them with profuse bleeding. Doctors eventually learned to treat the disease by giving patients factor VIII from donated blood.

But in the 1980s, HIV invaded the blood supply, and soon AIDS began to tear through the hemophiliac population.

Kazazian had come across three genetically unusual cases - boys with hemophilia whose factor VIII gene was disabled by an invading piece of stray DNA.

The invading DNA belonged to a specific category of the junk DNA called a transposable element. These had been observed in plants, where they had the power to act like a virus, copying themselves and jumping to new parts of the genetic code.

Most human transposable elements belong to a family called line1 elements. In total, Kazazian said,

we carry about 500,000 of them, making up a whopping 17 percent of human DNA, a major portion of the so-called junk. Most of these are inert, having lost their ability to cut and paste themselves to new locations.

But a few are still capable of jumping around and causing trouble.

How had these line1 elements gotten into the boys' factor VIII genes?

To figure it out, Kazazian was able to identify some unique stretches of code in the line1 sequence affecting one of the boys.

Using what is called a genetic probe, he was able to find the same sequence in a line1 element in the boy's mother, but it was in a different place, on Chromosome 22. (Human chromosomes are all assigned a number except the sex chromosomes, which are labeled X and Y.)

In her case, it caused no problem. Kazazian said he suspected that the line1 element jumped from her Chromosome 22 to the X chromosome either in the mother's egg cell or during an early stage in the development of the embryo that became the boy.

The boy was 10 years old when Kazazian made the discovery. His case was tragic, Kazazian said. During his teens he showed promise as an actor, snagging a major role in the movie *Lost in Yonkers.* But as a teenager, he acquired HIV from his treatment and died at 21.

Kazazian traced another hemophilia case to a jumping line1 element and went on to find line1 elements lurking behind a case of muscular dystrophy.

In 1994, he came to the University of Pennsylvania to head the genetics department. He stepped down as director in 2006 but still retains an active research agenda, supervising a coterie of scientists working on line1 elements in animals and humans.

He is intrigued now by the possibility that active line1 elements may copy themselves and invade DNA during human development, introducing genetic variation within the same person's DNA.

He said there were some tantalizing hints that in brain cells, this process could spawn variations in personality and temperament. In other parts of the body, it could leave some cells more vulnerable than others to cancer.

Kazazian said he was sure that his life had been channeled in part by his father's ordeal in Turkey. "I always knew he had wanted to become a doctor," he said. "I think he would have preferred that I go into medical practice . . . but eventually he realized I had to do my own thing."

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