Science AMA Series: I'm Haig Kazazian, a Johns Hopkins geneticist studying how "jumping genes" have helped to shape our understanding of genetic disease. AMA!

HopkinsMedicine$_{A}MA^{1}andr/ScienceAMAs^{1}$

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Abstract

Hi Reddit, my name is Haig Kazazian and I'm a geneticist at the Johns Hopkins University School of Medicine. For the past 27 years, I've been studying human genetics and I am passionately committed to understanding how "jumping genes," also known as retrotransposons, affect how genetic diseases manifest in my patients. These pieces of DNA are capable of moving around the genome and can potentially disrupt functional genes and lead to diseases like hemophilia and muscular dystrophy. Interesting fact about myself, in 1999, my colleague Arupa Ganguly and I received a "cease and desist" letter from Myriad Genetics, for studying the BRCA1 and BRCA2 genes because they held the patent. We became the first plaintiffs in the 2013 Supreme Court Case, which unanimously ruled that naturally occurring DNA sequences aren't patent eligible. More on the ruling here [http://www.scotusblog.com/2013/06/details-on-association-for-molecular-pathology-v-myriad-genetics-inc/]. I've recently published a review on the last fifty years of "jumping gene" research and you can read all about it here: [http://www.fasebj.org/content/31/9/3712.full]. I'll be back at 1pm ET today to answer your questions.

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REDDIT

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HOPKINSMEDICINE_AMA R/SCIENCE

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How does epigenetics play a role in retrotransposons?

Lord_Blackthorn

Epigenetics does play a role. It turns out that most of DNA methylation of our genome is in repetitive elements like the L1 or LINE-1 elements that make up about 30% or the genome. This methylation keeps L1s in check, turning down their "jumping". When DNA methylation of an element is turned way down, this allows the element to "jump". Other aspects of epigenetics must also be important in the "jumping" events.

Hi Haig - Thanks for doing this AMA, I am a fan of your research. A couple of questions for you:

- I've always wondered if the 'jumping' part of the retrotransposon lifecycle gets too much attention when it comes to how these elements impact disease. As I am sure you are aware, there are a number of other ways L1s and other retroelements can negatively impact host biology beyond insertional mutagenesis (i.e. they encode endonucleases, they are a transcriptional burden on the cell, they are repetitive and serve as templates for erroneous HDR events). Is the emphasis on the 'jumping' outsized, and if so, is it because it is just easier to demonstrate the harm due to insertional mutagenesis (by sequencing)?
- What are your thought on L1 activity in the brain? There was a bit of excitement about these elements contributing to neural mosaicism and neurodegeneration a few years ago. But questions

about methodology seems to have dampened the hype. Where do you see the field standing on this issue?

- Are L1 proteins presented in MHC-complexes in normal tissue, and if so, are they immunogenic? Asked another way, do T-cells target cells that express high levels of L1 protein, or are they tolerized to L1 proteins by negative selection in the thymus?

SirT6

On question 1, you are right that there are major effects of retrotransposons unrelated to their actual "jumping". Expression cahnges, addition of enhancers in the sequence, croosing over events leading to deletions or duplications of sequences. There is much more going on with these elements than their "jumping". Brain activity, hmm. My present thoughts are that it is clear that retrotransposition is going on in neurons, but at a low rate per cell-perhaps 0.5 to 1 insertion per cell. Of course, because since there are many neurons there may be billions of insertions in the brain, including in glia. However, whether these insertions lead to changes in behavior or have an effect on psychiatric disease is still very much up for discussion. On question 3, no they are not immunogenic as far as we know. They may promote an innate immune response, however. I have no knowledge about the second part of your question. However, I think not.

Good afternoon, how was lunch?

What're some scary realizations your team has had concerning gene research?

Thank you

lurking_digger

Lunch was fine. Nothing really scary from my point of view. This is biology. Lots of surprises making it fun to do the work.

Known origin, cause, transmission of jumping genes?

Any comparison whether they occur in the same gene locations for everyone?

Boleo

These "jumping genes" are really very old. They have been around for at least 500 million years-way before humans were around. They have been found in yeast and we have remnants of their jumps as debris and sequences for other uses in our genome. So even though over 30% of the genome is due to "jumpng genes" and we have over 500,000 L1 sequences, only about 100 or these L1 sequences are capable of "jumpng" still in any one individual, and the other 499,900 or so are dead and filling up the genome. Of the 100 active L1s in our genome, perhaps 90% or the "jumping" is due to only 5-8 or them. On the second question, we all have about 1000 human specific L1s, again most dead, that have been around for perhaps 200,000 years. These are all in the same place in everyone. However, many of the active ones are present only in a subset of the population, meaning they are what we call polymorphic. However, you probably have a different set of active polymorphic L1s than I do. So your active L1s are in a different genomic location from mine.

Hi and thanks for joining us today!

How big is the discovery of PNLDC1 for transposon science?

Is there real potential to use the transposon repair mechanism to disrupt spermatogenesis and act as a male birth control?

PHealthy

Sorry, I don't know about PNLDC1. I also don't know how transposon repair would work to disrupt spermatogenesis.

Hello and thank you for conducting this AMA!

How much of an impact do "jumping genes" and other mobile genetic elements have on the development of antimicrobial resistance?

Hitlers_Gas_Bill

The bacterial "jumping genes " are different from the ones that are active in mammals. Ours are retrotransposons that go through an RNA intermediate and are "copy and paste". Bacteria have DNA transposons that are "cut and paste". This means that in bacteria the DNA transposon is cut from one site and pasted into another site in the DNA. Antimicrobial resistance is often carried by a transposon. So the answer is YES they do have an impact on antimicrobial resistance.

Hi Dr. Kazazian,

I am a current graduate student about to start looking for postdoctoral positions. I want to stay in academia.

What advice do you have for someone who is at my stage of their career? If you could start investigating something right now other than jumping genes, what would it be?

Thanks!

rubber_ducky_

I'd say that it is important to find a good mentor for a postdoc, but probably the most important thing is that you work on something that really excites you. I was 50 when we found the first mobile DNA insertion in a human being causing hemophilia and it took me about 1 second to decide that I was going to shift my lab to work on mobile DNA. I found it very exciting that pieces of our human DNA could be copied and pasted in another genomic site. So find something that really interests you and then work hard to make contributions to the science. What would I work on-I think I'd stick to molecular genetics, but I'd probably wonder what field is not so populated but has a chance to boom, perhaps memory. However, I do think that the most important point is to go into a field that really excites you. There was essentially no genetics, especially human genetics, when I went into it 50 years ago. However, I thought that since we then knew that DNA was the genetic material, that the base was there, and there would be lots to learn. Cheers and good luck!

How are diseases caused by retrotransposons different/similar to diseases caused by translocations?

23523536

The disease caused by retrotranspsons are the same as other diseases. This is just another form of mutation. Retrotransposons make up about 1 in every 250 mutations so they are not a really common mechanism. However, since they can jump anywhere in the genome, they can cause any disease that

is due to defects in a single gene. So far we know of about 150 cases of different diseases, including cancer, due to retrotransposon insertions.

Hi Dr. Kazazian,

Thanks for doing this. How did you get started being a scientist? And what do you feel led you to study jumping genes?

bad_ape

I was always interested in puzzle solving. I went to medical school and trained in pediatrics because I really liked kids. I had my first research experience in a biochem lab at Dartmout Med School. However, while in med school I took a seminar class in genetics and really liked it, so after 2 years of peds training I went into genetics. At first I worked on a great problem with a wonderful mentor on fruit fly genetics. Then I got to go to Harvey Itano's lab at the NIH to work on hemoglobin regulation. I was recruited back to Johns Hopkins Pediatrics and started working on hemoglobin genetics and thalassemia, a globin disorder. After working out a lot of the mutations in thalassemia with Stuart Orkin at Harvard, I wnated to work on mutations in another disease due to a very large gene (globin genes are very small). We picked the factor 8 gene of hemophilai and collected 240 patients to study. Two of these patients had L1 insertions causing their disease so this is what geot me into "jumping gene" research". Another important point is that I've always had really outstanding trainees, grad students and postdocs, to work with and I've really enjoyed that so many of them have turned into stars in their fields. Hope this gives you a good idea of my enthusiasm for the sience and the people involved.