2013 Curt Stern Award Address[1]

John V. Moran[2,3,*]

Thank you, Haig, for the poignant introduction and kind words. I would also like to thank Jeff Murray, The American Society of Human Genetics (ASHG), the members of the Awards Committee, and especially Christopher Pearson. I first learned that I was the recipient of the 2013 Curt Stern Award from Christopher when I was on vacation with my family in San Francisco. I was pleasantly surprised and, frankly, was rendered speechless. For those of you who know me, you probably know that it takes a lot to render me speechless. I am truly honored and humbled to be the recipient of this prestigious honor.

As Haig so elegantly outlined, Curt Stern was an outstanding scientist who conducted genetic studies in model organisms to gain fundamental insights about basic cellular processes. Namely, he used the fruit fly, *Drosophila melanogaster*, to demonstrate crossing-over between homologous chromosomes[1] shortly after Harriet Creighton and another one of my scientific heroes, Barbara McClintock, demonstrated the same phenomenon in maize.[2] Stern subsequently demonstrated that mitotic recombination could lead to the generation of somatic mosaics,[3] which is a topic that I will touch upon later in the talk. In addition to being an outstanding basic scientist, Curt Stern was also a fabulous educator. During my career, I have found that excellent communication skills and the ability to do outstanding basic science research often go hand in hand.

While preparing this talk, I asked Tom Glover, my neighbor in the Department of Human Genetics at the University of Michigan, some questions about Curt Stern's career. Tom shared with me his copy of the third edition of Curt Stern's seminal textbook,[4] *Principles of Human Genetics*. He pulled the text off his bookshelf, gave it to me, and then took it back. Tom paged through the text while recounting how he used it during graduate school. Nostalgically, Tom repeatedly told me what Stern's textbook meant to him and how influential it was to a generation of human geneticists. I never met Curt Stern, but it was touching to hear Tom talk about him so fondly. It clearly put this award in context.

Over the years, my laboratory has studied what many probably still consider to be "junk" DNA. However, through the work of pioneers in the field, such as Maxine Singer and Haig Kazazian, and the subsequent completion of the human genome reference sequence, it is now evident that our genomes are replete with sequences derived from "jumping genes" known as transposable elements.[5] Indeed, long interspersed element 1 (LINE-1 or L1) retrotransposons and short interspersed elements (such as Alu), which are sequences mobilized by the LINE-1-encoded proteins, comprise approximately one billion bases, or almost one-third, of human genomic DNA (reviewed in Beck et al.[6]). A major tenet of our laboratory is that a fundamental understanding of LINE-1 biology is necessary for elucidating the forces that have shaped the structure, evolution, and perhaps function of the human genome. Over the past 15 years, my laboratory has focused on answering three basic scientific questions: (1) How do LINE-1 retrotransposons mobilize (i.e., retrotranspose) to new genomic locations? (2) What is the

[1]This article is based on the address given by the author at the meeting of The American Society of Human Genetics (ASHG) on October 26, 2013, in Boston, MA, USA. The audio of the original address can be found at the ASHG website.

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impact of LINE-1 retrotransposition on the human genome? (3) What host factors regulate and/or restrict human LINE-1 retrotransposition?

Today, I would briefly like to discuss my scientific journey by building upon themes discussed earlier at this meeting in wonderful talks by Jeff Murray, Jessica Davis, Kurt and Rochelle Hirschhorn, and Aravinda Chakravarti. In particular, I would like to emphasize (1) the importance of mentors, (2) the importance of picking an interesting problem to study—emphasizing the idea that beauty is in the eye of the beholder—and (3) the importance of a supportive scientific environment. I have been fortunate to have outstanding mentors throughout my career and have benefitted tremendously from the scientific environments that they created in their laboratories. I continually try to provide those same opportunities for my trainees—honoring my previous mentors by "paying it forward."

I originally became interested in studying transposable elements after reading a 1985 *Cell* paper, entitled "Ty Elements Transpose through an RNA Intermediate," by Jef Boeke.[7] In brief, the baker's yeast, *Saccharomyces cerevisiae*, harbors a class of retrotransposons known as Ty elements, which structurally resemble retroviruses. However, because Ty elements lack an envelope gene that is required for exiting the cell, they are relegated to a fate of intracellular replication. Through a series of well-controlled, elegant genetic experiments, Jef designed an assay to show that Ty elements could "jump" to new locations via an RNA intermediate—through a process known as retrotransposition. He and his colleagues subsequently used that assay in conjunction with molecular genetic, genomic, and biochemical approaches to gain a detailed understanding of Ty retrotransposition. Early in my graduate career at The Ohio State University, Jef gave a seminar detailing his scientific findings. Afterward, he and two of my colleagues went out for dinner, drank some beer, and discussed his research in depth. It was then that I realized I wanted to pursue transposable-element research. Jef is kind and gracious; he has served as a mentor, colleague, and friend over the years—I am thankful for his camaraderie.

My path to graduate school was somewhat indirect. I graduated from Rochester Institute of Technology (RIT) in 1986 with high honors in chemistry. I had applied to various medical schools in New York State but was not granted admission. So, late in the season, I needed an alternative plan and began to look at graduate schools throughout the country. However, the application deadlines had passed at many schools. Fortunately, I was accepted into The Ohio State University Biochemistry Program (OSBP).

My initial plan at Ohio State was to focus on biochemical research. One of the requirements of OSBP was to take a course in genetics or molecular genetics to help broaden one's academic knowledge base. Thus, I enrolled in a graduate-level molecular genetics course. In the introductory lecture, the instructor, Dr. Philip (Phil) Perlman, gave the class a list of approximately 50 genetic and molecular genetic terms and said (I paraphrase), "If you don't know most of these terms, you may not do well in the course." I only knew a few terms—actually, I knew one fewer than I thought because I thought a library was a place where you withdrew books. I spoke with Phil after the class. He assured me that I would benefit from taking the course and would do well if I worked hard.

Phil was an outstanding lecturer and teacher. I did well in his course and subsequently approached him about conducting a research rotation. We talked about the genetic research being conducted in his laboratory, and it became evident that my knowledge of some basic concepts (e.g., mitochondrial genetics, genetic mapping, and crossing-over) was lacking. Phil also talked to me about a project on intron splicing. Having completed my undergraduate degree in chemistry, I understood that splicing occurred by a two-step *trans*-esterification reaction, which I guess impressed Phil because he generously allowed me to conduct a research rotation. My initial projects focused on genetic mapping and the characterization of respiratory-deficient mutants in yeast mitochondrial DNA. I liked genetics, took to it quickly, and later was a teaching assistant for an upper-level undergraduate genetics class. In a theme that repeated during my graduate and postgraduate studies, Phil, like a transposable element, moved to the University of Texas Southwestern Medical Center (UTSW) in Dallas. I completed my Master's degree at Ohio State and then moved with Phil to UTSW to complete my doctoral studies, which focused on characterizing mobile introns in yeast mitochondrial DNA.

When I entered graduate school, it was widely thought that introns were "junk" RNA. Simply stated, introns represented sequences that needed to be removed or spliced from premessenger RNAs to produce protein-coding messenger RNAs. However, through the work of pioneers in the field, including Tom Cech, Alan Lambowitz, Piotr Slonimski, Bernard Dujon, Marlene Belfort, Ron Butow, and Phil Perlman, it became apparent that certain introns, as well as other cellular RNAs, could function as enzymes—a discovery that allowed Tom Cech to share the 1989 Nobel Prize in Chemistry with Sidney Altman.[8] Moreover, it was found that some fungal mitochondrial introns encode proteins and that some of those proteins catalyze intron splicing and/or intron mobility.[9,10] Indeed, certain fungal mitochondrial introns were found to be mobile genetic elements! The above vignette proved illustrative in my career because it provided a direct example of how one's misperception of "junk" can change with dedicated efforts and outstanding experimentation.

I had the good fortune in Phil's laboratory to be an author on a number of papers that focused on elucidating mechanistic features of intron mobility in yeast mitochondria.[11–14] Through trial and error, I also learned about the art of experimental design, the importance of conducting well-controlled experiments, and how to critically analyze and interpret data. I still frequently relay one of

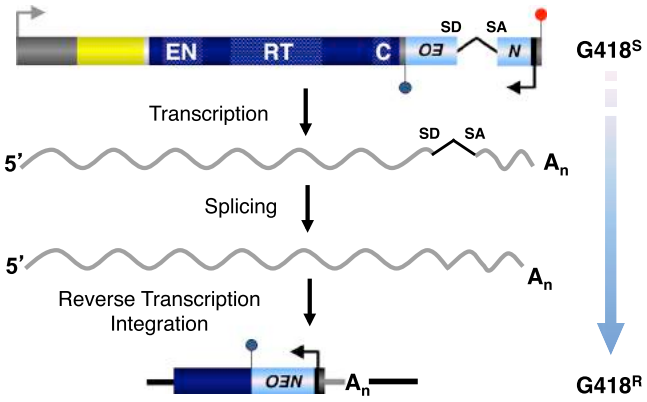

Figure 1. A Schematic of the LINE-1 Retrotransposition Assay
A full-length LINE-1 contains 5′ and 3′ UTRs (gray rectangles). The 5′ UTR contains promoter activity (gray arrow). The two open reading frames, ORF1 and ORF2, are depicted by maize and blue rectangles, respectively. A polyadenlyation signal (red lollipop) is present at the 3′ end of the LINE-1 construct. The LINE-1 3′ UTR is disrupted by a *NEO* retrotransposition indicator cassette. The cassette comprises a backward copy of a *NEO* expression cassette that contains its own promoter (black arrow) and polyadenylation signal (blue lollipop). *NEO* is also interrupted by an intron (SD, splice donor site; SA, splice acceptor site) in the same transcriptional orientation as the LINE-1. This arrangement ensures that *NEO* expression can only be activated upon LINE-1 retrotransposition, allowing cells to subsequently grow in the presence of the drug G418. The rationale of the assay and other details are provided in the text. This figure was adapted from Moran et al.[20]

Phil's mantras, "Trust your data," to my trainees. I learned many life-long lessons from Phil and will always be thankful for his mentorship, time, and patience.

While I was in graduate school, Phil told me about the seminal work being conducted on human LINE-1 elements in Haig Kazazian's laboratory at the Johns Hopkins School of Medicine. I had the pleasure of seeing Haig present the findings from his laboratory during a seminar at Ohio State. As was the case for intronic RNA, it was thought that much of the human genome consisted of "junk" DNA, that much of the "junk" was derived from transposable elements that had lost the ability to move, and that these transposable element sequences could simply be considered molecular fossils.

The prevailing view that LINE-1 elements were simply "junk" DNA radically changed in 1988. In a seminal paper, Haig screened for mutations within a cohort of 240 young boys afflicted with the X-linked recessive disorder hemophilia A.[15] He identified two patients who contained independent de novo LINE-1 retrotransposition events in exon 14 of *F8*. These data unequivocally demonstrated that LINE-1 retrotransposition could lead to sporadic cases of human disease. Through a series of elegant, landmark experiments, Beth Dombroski, a talented postdoctoral researcher in Haig's laboratory, subsequently identified a full-length LINE-1 element that most likely spawned the mutagenic LINE-1 insertion in one of the hemophiliac patients.[16] Thus, Haig's lab was armed with the tools needed to study human LINE-1 retrotransposition.

Because the reverse-transcriptase proteins encoded by group II introns (which I studied in graduate school) and human LINE-1s are evolutionarily related, I thought that pursuing postdoctoral studies with Haig would both represent a natural extension of my graduate work and provide me with a foray into human genetic research. After a slight delay in completing my graduate studies, I moved to Johns Hopkins in 1994. In a classic case of "ignorance is bliss," I only knew Haig (I subsequently dubbed him "The Big Guy") from his LINE-1 work. I did not know that he had high standing in the field of human genetics!

Almost immediately after my arrival, Haig transposed to Philadelphia to become the chair of the Department of Genetics at the University of Pennsylvania School of Medicine. Like a mobile element, I commuted back and forth between Baltimore and Philadelphia (and squatted for a while in Jef Boeke's laboratory) until my wife, Robin, was able to arrange a transfer of her job at the Environmental Protection Agency from Washington D.C. to Philadelphia.

My time in Haig's laboratory was wonderful. Haig always answered my many, many questions and continually taught me the history of human genetics throughout my postdoctoral fellowship. In return, I brought experience from Phil's laboratory, which allowed me to develop a genetic assay to study LINE-1 biology. Simply stated, Haig has been an exceptional mentor and friend throughout the years.

To design an assay for LINE-1 retrotransposition, we borrowed genetic tricks originally developed by Thierry Heidmann and Joan Curcio.[17,18] In brief, I tagged the 3′ UTR of a full-length LINE-1 with a retrotransposition indicator cassette that we had obtained from Dixie Mager.[19] The cassette consisted of a backward copy of neomycin phosphotransferase (*NEO*) equipped with its own promoter and polyadenylation signal (Figure 1). *NEO* was also interrupted by an intron, which is in the same transcriptional orientation as the LINE-1 element. The rationale of the experiment was as follows. If transcription is initiated from the promoter driving *NEO* expression, the intron cannot be spliced because it is in the wrong polarity. However, if transcription is initiated from either the native LINE-1 promoter or a heterologous RNA polymerase II promoter driving LINE-1 transcription, the intron can be spliced from LINE-1 RNA. Translation of the resultant LINE-1 mRNA would then allow the production of LINE-1-encoded proteins (ORF1p and ORF2p); *NEO* would not be translated from the LINE-1 mRNA because it was present in a "backward" orientation. However, if the LINE-1 mRNA retrotransposed—that is, if it were reverse transcribed and integrated at a new chromosomal location—*NEO* could become activated, allowing cells to grow in the presence of the *NEO* analog, G418. In sum, our strategy allowed us to score human LINE-1 retrotransposition events by simply counting G418-resistant cells.

With the help of Roger Kennett, who taught me tissue culture, we carried out our experimental assay (Figure 2).

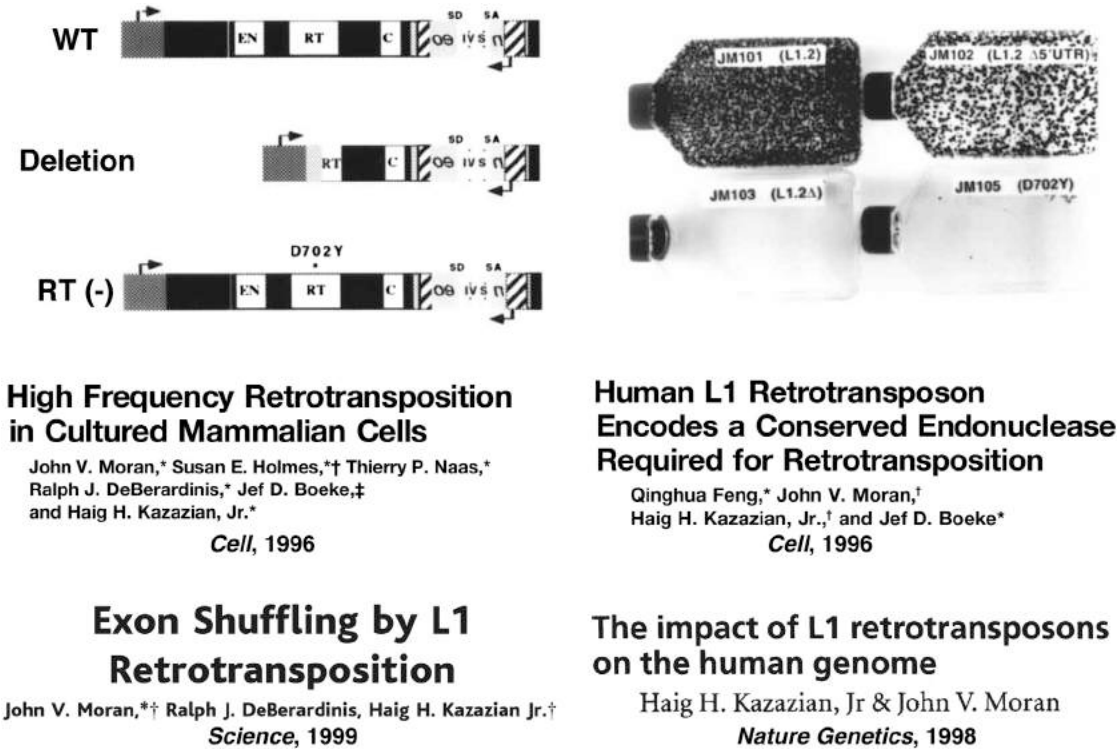

Figure 2. Results from the LINE-1 Retrotransposition Assay
Top: Wild-type LINE-1 elements can readily retrotranspose in cells, whereas a deletion mutant and a reverse-transcriptase mutant cannot retrotranspose. This figure was adapted from Moran et al.[20]
Bottom: The titles of papers published during my time in Haig Kazazian's laboratory.

To our surprise, we found that full-length LINE-1 constructs readily retrotransposed in cells.[20] By comparison, constructs that contained either a large deletion of LINE-1 coding sequence or a missense substitution in the LINE-1 ORF2p reverse-transcriptase active site were unable to undergo retrotransposition. Subsequent experiments revealed that the retrotransposition events derived from our engineered constructs contained LINE-1 structural hallmarks (e.g., they ended in a poly(A) tail, were 5′ truncated, and were flanked, in most cases, by target-site duplications) and uncovered additional functional domains required for retrotransposition in both ORF1p and ORF2p.[20,21] Our results clearly demonstrated that the LINE-1-encoded proteins are required for retrotransposition and, by analogy to work conducted on a related retrotransposon in the silkworm, *Bombyx mori*, by Tom Eickbush's laboratory,[22] suggested a plausible mechanism for LINE-1 retrotransposition.

After developing this assay, we published a series of papers (Figure 2) that helped decipher the mechanism of L1 retrotransposition and its impact on the human genome.[20,21,23–25] Importantly, I came to the realization that I could actually obtain gainful employment by studying something that I really liked! I also realized that it would be good to have a real job, with which my wife, Robin, agreed, because my oldest son, Joshua, was born in January of 1998.

My experience in Haig's laboratory had a great influence on my career, and I knew that I wanted to continue doing human genetic research. Thus, in 1998, I accepted an assistant professor position in the Department of Human Genetics at the University of Michigan Medical School, which was founded by Dr. James Neel. Notably, Jim trained with Curt Stern during his time at the University of Rochester,[26] a fact that gives this award special meaning to me.

During my time at Michigan, I have been fortunate to have outstanding colleagues both inside and outside the University. David Ginsburg and Tom Gelehrter originally recruited me to Michigan. When I attended my first Department of Human Genetics retreat, Tom had the faculty take a Myers-Briggs personality test. I learned that I scored in an extroverted leadership quadrant. In contrast, almost all the other faculty were diametrically opposed—they scored in an introverted leadership quadrant. I wondered, "My gosh, what did I get myself into"? Upon reflection, I can only imagine what everyone else was thinking! I have been fortunate to have the full support of both David and Tom over the years, and their enthusiasm was instrumental in allowing me to start my career as an independent young scientist.

Others at Michigan have also served as mentors and supported my growth as an independent scientist. Sally Camper, my chair for the past 8 years, has been very

Figure 3. Pictures of My Laboratory over the Years

supportive. Importantly, Sally successfully recruited a number of outstanding young faculty members to the department, reinvigorating the spirit of Human Genetics at Michigan. I am pleased that she allowed me to run the search committee for 2 of those years. Gil Omenn and Martha Darling have been personally generous by endowing a Department of Human Genetics professorship, which I have been fortunate to hold for the past 3 years. Finally, I would like to acknowledge Miriam Meisler. Miriam has directed the National Institutes of Health-funded University of Michigan Genetics training program for many years. I have served as the associate director of that program since 2006 and will assume the directorship in 2014. I thank Miriam for her mentorship.

I have been fortunate to benefit from supportive environments in graduate school, as a postdoctoral fellow, and as a faculty member. Thus, I realize the importance of creating a supportive environment in my own laboratory. I have never wanted a lab of 30+ people. Instead, I wanted to create an environment that was large enough to reach "critical mass" but small enough that I could have a deep understanding of the research in the laboratory. I have always considered the lab a family and have been extremely fortunate to attract outstanding graduate and undergraduate students, postdoctoral fellows, and research assistants (Figure 3). Over the years, as in any family, my trainees and I have seen each other at the best of times and the worst of times. However, one of the most gratifying parts of being a mentor is to see your trainees gain admission to graduate or medical school, get outstanding postdoctoral fellowship opportunities, and obtain independent faculty positions. I am gratified that most of my trainees have been successful in achieving their goals.

I am pleased that our laboratory has made several important advances in understanding LINE-1 biology (Figures 4 and 5). On the mechanistic front, we followed up on previous studies by Gary Swergold[27] and identified LINE-1 5′ UTR sequences that were important for its transcription.[28] We further found that the second open reading frame of LINE-1 mRNA is translated in an unconventional manner[29] and established a biochemical platform to both detect and study the activities associated with the LINE-1-encoded proteins.[30–32]

In genomics-based studies, we demonstrated that LINE-1 is not simply an insertional mutagen but that its retrotransposition could lead to alterations of target-site genomic DNA.[33,34] These include the generation of intrachromosomal deletions via a single-strand-DNA-annealing mechanism, as well as more baroque, complex rearrangements that lead to small intrachromosomal inversions by a synthesis-dependent strand-annealing mechanism that, in certain aspects, resembles yeast mating-type switching. Indeed, it was gratifying that events we initially detected in cultured cells were also detected at some frequency in the human genome. Moreover, in collaborative efforts with Richard Badge and Evan Eichler, we have used modern genomic approaches with our cell-culture assay to demonstrate that there could be millions of retrotransposition-competent LINE-1 sequences in the extant human population.[35]

We serendipitously discovered an alternative, endonuclease-independent mechanism of LINE-1 retrotransposition, which suggests that LINE-1 sequences could parasitize genomic lesions; this would essentially allow for their repair through an RNA intermediate.[36] Interestingly, using cultured cell models, we found that

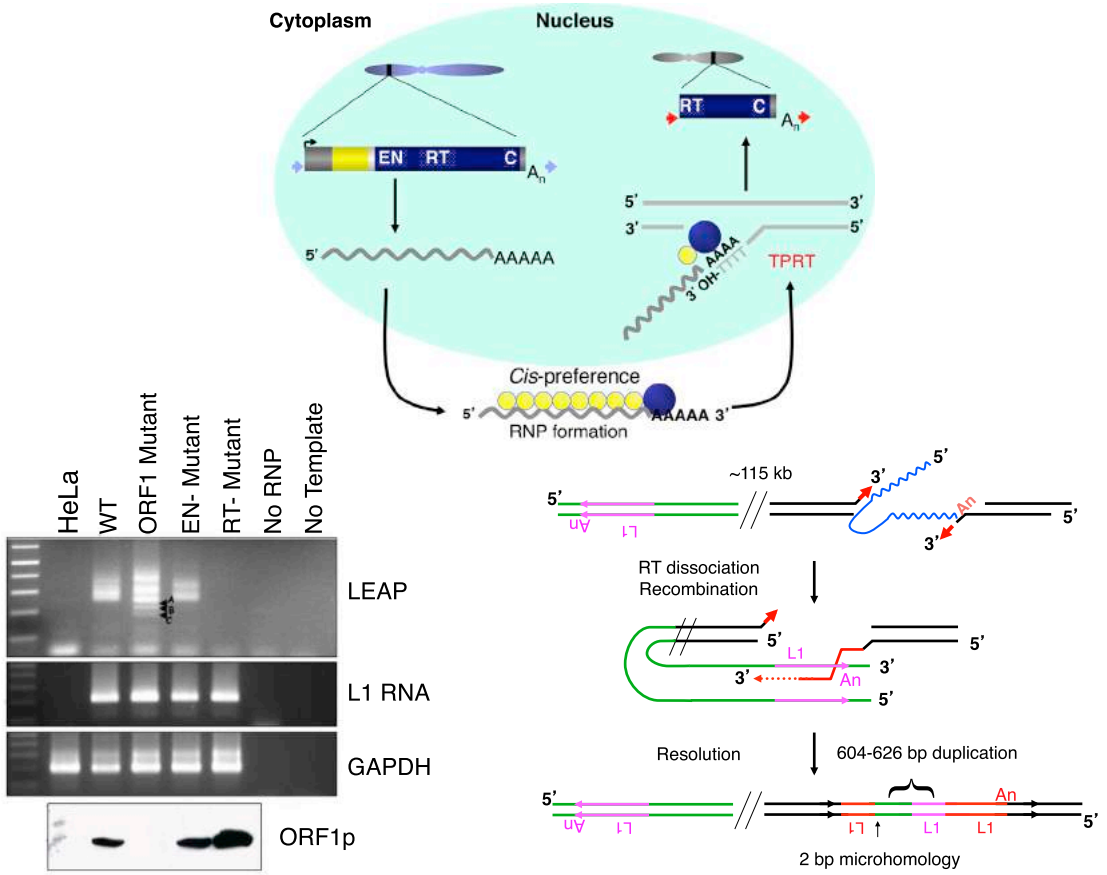

Figure 4. Representative Results Published from My Laboratory over the Years: The Mechanism of LINE-1 Retrotransposition
Top: A simplified working model for LINE-1 retrotransposition (reviewed in Beck et al.[6]). This figure is from Deanna Kulpa.
Bottom left: Results from a biochemical experiment show that ribonucleoprotein particles derived from cells transfected with a wild-type engineered human LINE-1, an ORF1p RNA binding mutant LINE-1, or an ORF2p endonuclease mutant LINE-1 contain reverse-transcriptase activity, whereas an ORF2p reverse-transcriptase mutant does not. This figure was reprinted with permission from Kulpa and Moran.[30]
Bottom right: An example of how LINE-1 retrotransposition can lead to structural variation in the human genome. This figure was adapted with permission from Gilbert et al.[33]

dysfunctional telomeres could also serve as substrates for endonuclease-independent LINE-1 retrotransposition events,[37,38] thereby highlighting mechanistic similarities between the catalytic subunit of telomerase and the LINE-1 reverse transcriptase.

Finally, we demonstrated that LINE-1s could retrotranspose in human embryonic stem cells.[39] In collaborative work with Fred (Rusty) Gage and Alysson Muotri, we demonstrated that LINE-1 retrotransposition could lead to somatic mosaicism in the brain.[40,41] The extent to which L1 retrotransposition affects the brain remains somewhat controversial; however, these data harken back to Curt Stern's research and strongly suggest that tissue-specific differences in LINE-1 retrotransposition could lead to somatic mosaicism. Time will tell whether somatic LINE-1 retrotransposition events in the brain represent a type of "genomic noise" or whether they can sometimes influence neuronal function.

Clearly, there has been an evolution of thought with regard to LINE-1 elements in the human genome. Before Haig's studies, LINE-1s were mostly regarded as "junk" DNA. His seminal findings led to the idea that there might be a number of active LINE-1 elements in the human genome and that their mobility could occasionally lead to disease. Now, we have come to the realization that active LINE-1 elements, which are present at low or even private allele frequencies, are alive and well in the human genome and that their mobility continues to influence the evolution, structure, and perhaps function of the human genome.

As with any field, there are several big questions that remain in LINE-1 biology. These include the following: (1) How often does LINE-1 retrotranspose? (2) When in development does LINE-1 retrotranspose? (3) What cell types accommodate LINE-1 retrotransposition? (4) Does LINE-1 retrotransposition contribute to cancer? (5) How does the host regulate and protect itself from unabated LINE-1 retrotransposition? We, along with the rest of the field, hope to get answers to these intriguing questions in the coming years.

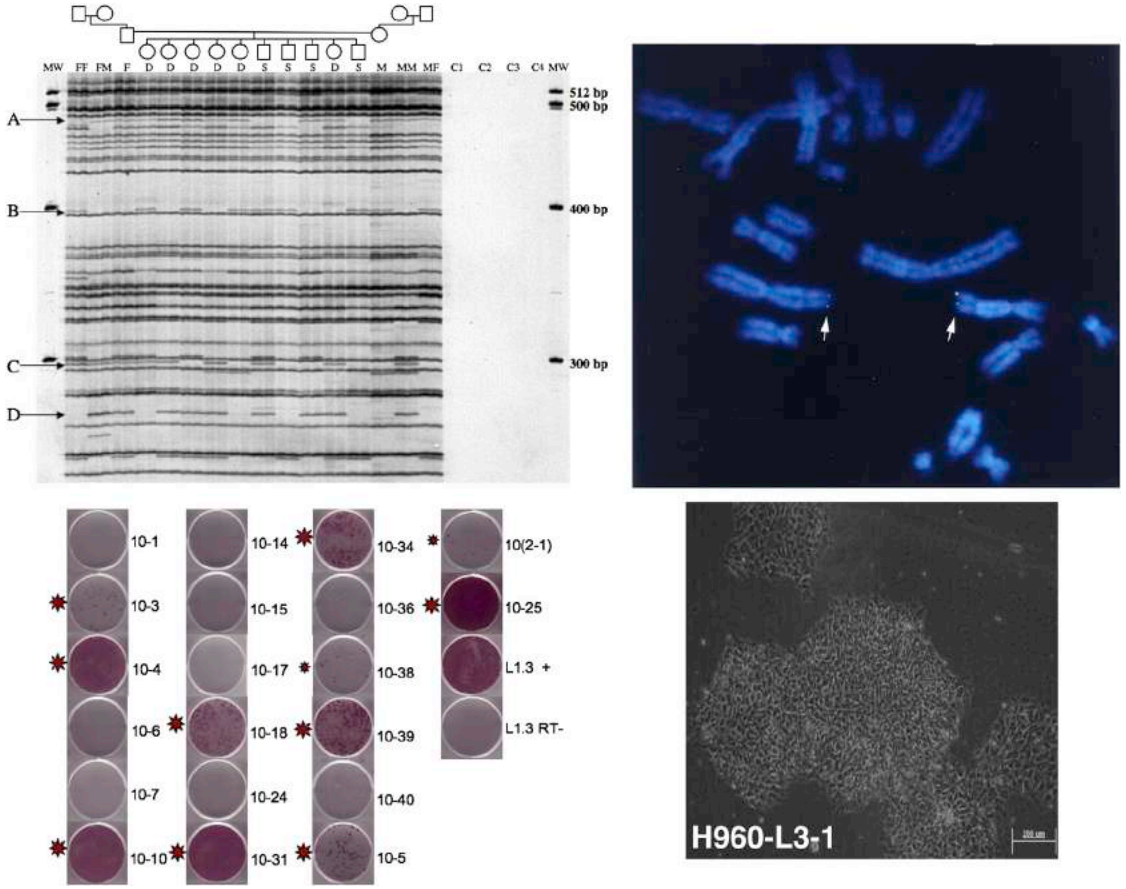

Figure 5. Representative Results Published from My Laboratory over the Years: The Impact of LINE-1 Retrotransposition on the Genome

Top left: Segregation of polymorphic LINE-1 elements in an extended pedigree. This figure was adapted from Badge et al.[42]
Top right: An image confirming that endonuclease-independent LINE-1 retrotranspositon can occur at dysfunctional telomeres in Chinese hamster ovary cells that lack p53 activity and are deficient in a component of the nonhomologous-end-joining DNA-repair machinery. This image was reprinted with permission from Morrish et al.[37]
Bottom left: The identification of active "hot L1s" from an individual genome.[35]
Bottom right: A human embryonic stem cell colony containing an engineered human LINE-1 retrotransposition event. This image was reprinted with permission from Garcia-Perez et al.[39]

To end, I would like to thank my family. Being half Irish and pretty much half Finnish, I am an interesting genetic mix—I have come to the conclusion that, for me, Irish is dominant. I would like to thank my mother, who in her quiet way has always been supportive of my education, dreams, and ambitions—she is a wonderful person. My father, who was a devout Catholic, taught me the values of hard work and the importance of an education. He passed away in 2001 from complications associated with type II diabetes. I applaud my ASHG colleagues, such as Mike Boenhke, who actively works on understanding the genetic etiology of type II diabetes—their efforts have special value to me. I thank my brother, Craig, who is bigger, stronger, and perhaps smarter than I am and has served as a New York City police officer for 22 years. I have always admired his honesty, hard work, and devotion to his family. Indeed, many of my childhood friends became police officers or held other public-sector jobs in New York City. I also thank my grandmother, who in her straightforward, stoic Finnish manner often asked (I paraphrase), "Why can't you finally get out of graduate school?"

Finally, I must thank my beautiful wife, Robin. I met Robin in 1986 only a few months before I graduated from RIT. In a moment of clarity, I realized that she was special and that I wanted to spend my life with her. Our relationship involved quite a bit of transposition. We commuted between Columbus and Rochester to visit each other while I was in graduate school and then between Dallas and Columbus after I moved to UTSW with Phil. Although this took effort on both our parts, it has worked out fabulously. We have three wonderful children: Joshua, Jessica, and Ethan (Figure 6). It is a blessing to have healthy children; watching them grow has been one of the greatest pleasures of my life. Having three kids and balancing two careers can be a challenge at times. However, I would rather have an exciting, sometimes hectic life than a boring one. Simply stated, if it were not for the unconditional love and support of Robin and

Figure 6. A Picture of Me, My Wife, Robin, and My Children, Joshua, Jessica, and Ethan, at the Grand Canyon

my family, I would not have enjoyed the scientific success I have had in my life. I am a lucky man. Thank you again for this honor.

Acknowledgments

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