# Mobile elements:

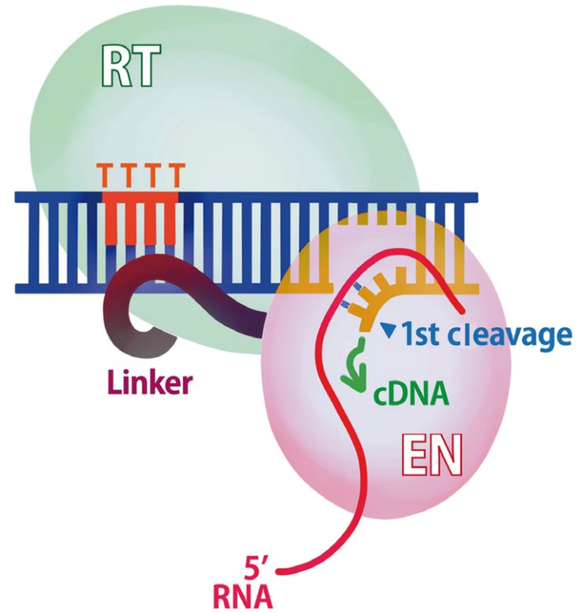
## Hidden architects of the Genome

*Professor Kazuhiko Ohshima from the Nagahama Institute of Bio-Science and Technology, Department of Bioscience, centres his research on mobile genetic elements. These elements have gained recent notoriety in the scientific community for their involvement in genome restructuring. Certain mobile elements have expansive family trees reaching back to the origins of the first eukaryotic cell; those that led to human life and other life on Earth. Professor Ohshima investigates the mechanisms by which these "jumping genes" flit between different species over different scales of evolutionary time.*

In 1951, Nobel prize winner Barbara McClintock discovered the first mobile elements in maize. During the 1950s, McClintock built upon her work and reported her findings to the wider scientific community. At this time, little was known about these mobile genetic elements and so many researchers dismissed and ignored them until the late 1960s-70s when they were discovered again, but this time in bacteria and yeast. A large part of the scientific community regarded regions of the genome populated by repetitive sequences (inclusive of mobile elements) as "junk DNA". The evolutionary importance of such elements has only been recognised since the beginning of the 21st century. Research since this time has grown with the purpose of understanding their role in the evolution of the genome and by extension the evolution of species across all domains of life. These mobile elements have propagated themselves over a vast molecular map that comprises the family tree connecting all life on Earth; from plants, fungi, bacteria, to mammals including humans. Although these elements do not code for what are deemed the most important regions of DNA; used to generate proteins for constituting and maintaining an organism, they constitute a large proportion of the genomes of certain plant and mammalian species. In humans, 1.5% of DNA is comprised of a proposed 20,000 -25,000 protein-coding sequences. Nearly 26% is comprised of non-coding DNA and the remaining 45% composed of transposable elements. Professor Ohshima focuses his research on elucidating the evolutionary journey of these mobile elements, relationships between mobile element families, their mechanisms of intra and inter genome movements and future uses in academic and medical research.

### JUMPING GENES

Mobile elements or transposons are so named because of their ability to move. They are pieces of genetic sequence that can move about the genetic landscape and target for themselves a new location. There are two classes of mobile genetic elements; determined by the way they move from one genetic location to another. Class I elements use a ribonucleic acid (RNA) intermediate to transpose from one location to another. RNA is an important molecule found in cells that acts as a mediator of cellular communication from DNA to protein production. Without RNA, important proteins cannot be produced that are vital for cellular and at large, whole organism functioning. Class I elements include long terminal repeat (LTR) retrotransposons, endogenous retroviruses, long interspersed elements (LINEs), short interspersed elements (SINEs) and non-autonomous elements known as processed pseudogenes (PPs). Class II elements move or transpose directly from one area of DNA to another without the need of an RNA intermediate. Elements that move in this fashion include DNA transposons and miniature inverted-repeat transposable elements. These elements by what is described as a simple "cut and paste" method. Active class II elements encode an enzyme called transposase which allows the element to move or "jump" to the new site. For both class I and class II elements, upon integration into a new genomic site, duplications of sequence at these target sites can occur. The length of these target site duplications (TSDs) are often characteristic of a particular mobile element.

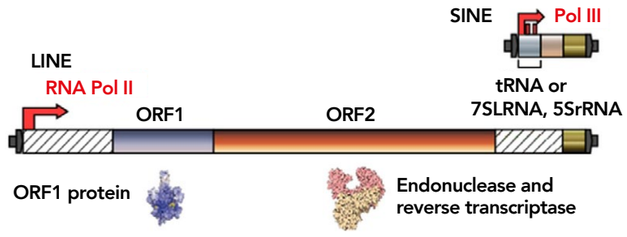



Model of the genomic integration machinery of RTE-related retroposons. The RTE protein binds to a DNA region containing a stretch of Ts upstream of the cleavage site, and cuts a phosphodiester bond approximately one helical pitch downstream of the stretch of Ts. Microsatellite-like sequences in the 3′-end of the template RNA for reverse transcription influence cleavage site selection by the RTE EN and/or facilitate the initiation of reverse transcription through base-pairing. Illustration taken from: 'Cross-Kingdom Commonality of a Novel Insertion Signature of RTE-Related Short Retroposons'. *Genome Biol Evol*. 2018;10(6):1471-1483. doi:10.1093/gbe/evy098.

### READING BETWEEN THE LINES

In humans, LINEs and SINEs comprise over 30% of the genome; a large amount compared with other transposable elements. Both SINEs and LINEs use a copy and paste method to insert themselves into another area of the genome. SINEs are non-autonomous and are characterised by a certain type of RNA sequence. One of the most famous SINEs called the Alu element is derived from 7SL RNA in the human genome. In other species of plants and animals, SINEs are known to consist of "head" (originating from tRNA), body and "tail" (LINE origin). During the process of protein synthesis, tRNA is responsible for delivering building blocks called amino acids to a complex molecular machine called ribosome in order to build a sequence of amino acids that then forms a protein in the cell. The tRNA-derived SINE head DNA drives the production of full-length SINE "replicas" (RNA). This means that the SINE element can be subject to multiple rounds of transposition. Professor Ohshima highlights the finding that SINEs possess common genetic sequences of homology with LINEs present at their "tail" end in plants and animals. In one study, Professor Ohshima found that the last 100 nucleotide bases of tobacco TS SINE to be nearly identical with a LINE found in the genome of the same Solanaceae plant. LINE-encoded protein is known to specifically recognise the sequence near the tail end of the LINE RNA to start "copy and paste", the homology between SINEs and LINEs suggests that each SINE element recruits the enzymatic machinery for transposition from the corresponding LINE through this common tail. Professor Ohshima and colleagues also discovered other LINE/SINE pairs within the turtle (chelonian) and salmonid genomes sharing homologous tail sequences.

**Mobile elements have propagated themselves over a vast molecular map that comprises the family tree connecting all life on Earth.**




A schematic representation of a SINE and a LINE that have the same 3′-end sequence. Three-dimensional protein structures are taken from the L1-encoded ORF1 protein and the reverse transcriptase of human immunodeficiency virus type 1. This was previously published in 'RNA-Mediated Gene Duplication and Retroposons: Retrogenes, LINEs, SINEs, and Sequence Specificity', *International Journal of Evolutionary Biology*, Volume 2013, Article ID 424726, 16 pages, http://dx.doi.org/10.1155/2013/424726 and is under the Creative Commons Attribution License (CC BY 3.0).

### PARASITES OR MUTUALISTIC SYMBIONTS?

Professor Ohshima and his research team have previously characterised a type of SINE called CHR-1 SINEs present in cetaceans, ruminants and hippopotamuses. One member of this SINE integrated into a coding region of bovine messenger RNA (mRNA).



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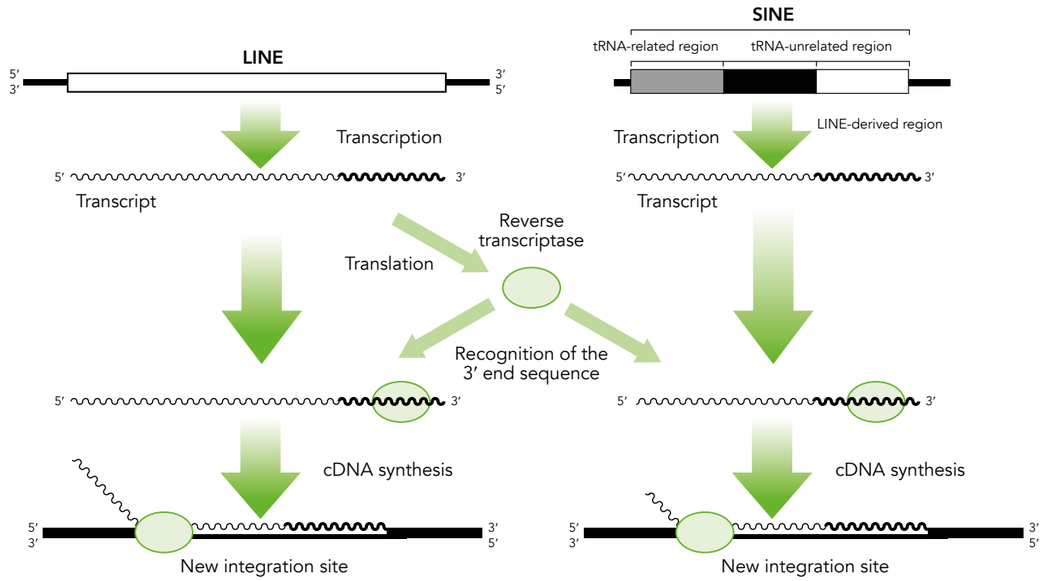
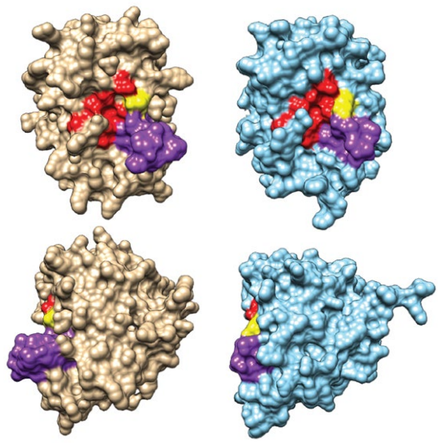



Enzymes required for the retroposition of a tRNA-derived SINE are presumably provided by a corresponding LINE. Transcripts of the SINE are recognised through the common tail sequence by a reverse transcriptase generated from the corresponding LINE, and they are reverse transcribed into cDNA by the target DNA-primed mechanism adopted by LINEs.

***In humans, LINEs and SINEs comprise over 30% of the genome; a large amount compared with other transposable elements.***

This mRNA/SINE chimera is translated into a protein product that plays a critical role in signal transduction involving control of neurotransmitter release. In other studies, Professor Ohshima and colleagues discovered a simultaneous burst of a type of SINE (Alu element) and PP formation in the genome of ancestral primates at approximately 40-50 million years ago. The finding suggests that the explosion of mobile elements at this time along with a change in the structure of the genome may have contributed to the radiation of higher primates. In a recent study by Ms Nishiyama and Professor Ohshima, they discovered definitively that Au SINEs in the genomes of flowering plants shared TSDs located in LINEs of a particular group or clade called RTE. In recent studies, RTE-clade LINEs have been found to undergo frequent horizontal transfer (HT). This is in opposition to a common understanding of the "vertical" transfer of these gypsies of the genome from one generation to the next within a particular species lineage. This HT involves the movement of genetic information along with a caravansary of mobile genetic elements between different species. Ms Nishiyama and Professor Ohshima propose that a unique motif sequence within the tail end of RTE-clade LINEs allows them to target a similar motif sequence within new host genomes. This may allow them to travel between genomes of different species. Professor Ohshima and his team of researchers are leading the way in elucidating the mechanisms underlying mobile element movement within and between species. Knowledge of the mechanisms of mobile element movement will advance research in gene editing for medical treatment and provide a new insight into the evolution of species through symbiosis between host and mobile element genomes.




Comparison of the 3D structure of EN domains from soybean RTE and human L1. Space-filling representation of a 3D model of soybean RTE-EN constructed using human L1-EN as a template. The beta-hairpin loop of soybean RTE (cyan; right) and L1 (light brown; left) is represented in purple. The catalytic core and D229Q substitution are denoted in red and yellow, respectively. The lower images show left side views of the upper images. For reference, the DNA cleavage strand would be positioned vertically with the 5′-end at the top and the 3′-end at the bottom. Illustration taken from: 'Cross-Kingdom Commonality of a Novel Insertion Signature of RTE-Related Short Retroposons.' *Genome Biol Evol.* 2018;10(6):1471-1483. doi:10.1093/gbe/evy098.



# Behind the Research

## Professor Kazuhiko Ohshima

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## Research Objectives

Professor Ohshima focuses his research on elucidating the evolutionary journey of these mobile elements, relationships between mobile element families, their mechanisms of intra and inter genome movements and future uses in academic and medical research.

## Detail

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**Bio**

Ohshima received his PhD in Molecular Biology, Tokyo Institute of Technology in 1995. He later went on to become Assistant professor Tokyo Institute of Technology, 1996 -1997 to then become a lecturer from 1997-2004. Since 2004, he has been associate professor at Nagahama Institute of Bio-Science and Technology.

**Collaborators**

- Eri Nishiyama: Co-author, graduate student (alumna)
- Norihiro Okada: Professor at Tokyo Institute of Technology

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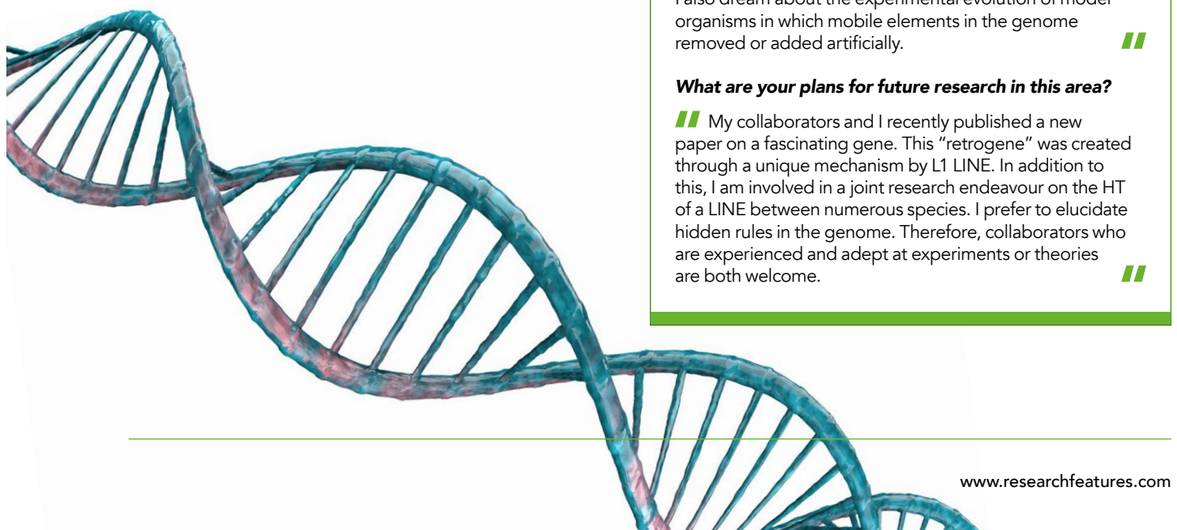

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## Personal Response

***What role are mobile genetic elements likely to play in future medical and experimental research?***

"Mobile elements have been studied for use as experimental tools such as mutagens, gene delivery vectors and genome engineering enzymes. This is one direction.

Epigenetic control of mobile elements is attracting researcher's attention. Knowledge of this area is growing rapidly. Some kinds of RNAs from mobile elements are found specifically in germ cells, ES cells, iPS cells, and cancer cells. Research for such elements may play significant roles in future medical research.

I also dream about the experimental evolution of model organisms in which mobile elements in the genome removed or added artificially."

***What are your plans for future research in this area?***

"My collaborators and I recently published a new paper on a fascinating gene. This "retrogene" was created through a unique mechanism by L1 LINE. In addition to this, I am involved in a joint research endeavour on the HT of a LINE between numerous species. I prefer to elucidate hidden rules in the genome. Therefore, collaborators who are experienced and adept at experiments or theories are both welcome."