

# From the “RNA World” to Brain Complexity: Generation of Diversity

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“To many neuroscientists one pyramidal cell is just like another.  
I, on the contrary, believe that it is important to  
distinguish the many types (and probably subtypes) of  
pyramidal cells. One can often see that two pyramidal  
cells look quite different.”

Francis Crick

In *The Impact of Molecular Biology on Neuroscience* (1999)

“I believe there is little reason to question  
the presence of innate systems that are  
able to restructure a genome.”

Barbara McClintock

In *The Dynamic Genome: Barbara McClintock's Ideas  
in the Century of Genetics* (1992)

## Summary

The recent finding that LINE-1 (Long Interspersed Nucleotide Elements-1, or L1) retroelements are active in somatic neuronal progenitor cells has provided a potential additional mechanism for generating neuronal diversification. L1 retrotransposition in the nervous system challenges the idea of static neuronal genomes, adding a new element for neuronal plasticity. Long dismissed as selfish or “junk” DNA, retroelements are thought to be intracellular parasites from our distant evolutionary past. Together with their mutated relatives, retroelement sequences constitute 45% of the mammalian genome, with L1 alone representing 20%. The fact that L1 can retrotranspose in a defined window of neuronal differentiation, changing the genetic information in single neurons in an arbitrary fashion, could allow the brain to develop in distinctly different ways. These characteristics of variety and flexibility may contribute to the uniqueness of an individual brain. However, the extent of the impact of L1 on the neuronal genome is unknown. In this chapter we will discuss the potential influence of L1 retrotransposition during brain development and the evolutionary pressures that may have selected this unexpected machinery of diversity in neuronal precursor cells. The characterization of somatic neuronal diversification will not only be relevant for the understanding of brain complexity and neuronal organization but may also shed

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light on the differences in cognitive abilities, personality traits and many psychiatric conditions observed in humans.

## Introduction

There are several ways to study brain complexity. Perhaps the broadest view is to analyze the brain's action or its consequences. However, one could take a physiological approach and investigate how different regions of the brain produce a specific task. Others may try to understand the organization and rules of neuronal networks, or how the neural cells are connected to each other through synapses, in a systematic manner. Then, there are the cellular and molecular views. For those views, the ultimate characteristics of a single neuron are present inside the cell and how genes and molecules react to outside stimuli, from the environment or from the interaction with other cells. This reductionist approach will certainly not explain how the brain works, but may provide the necessary tools for understanding how the different levels of organization co-exist to generate perception, action, feelings, memories and thoughts.

It has been known for more than a century, through the work of Camillo Golgi and Santiago Ramon y Cajal, that neurons are specialized cells with a huge diversity of shapes and connections. It is estimated that the human brain contains more than 10 000 different morphological types of neurons. However, neuronal diversity cannot be defined only by morphology or anatomic position. Similar cells, located at the same brain region, may have distinct electrophysiological properties and unique connection within other neurons. Moreover, neurons are extremely plastic cells, allowing extraordinary response upon micro and macro environmental stimulation. Any attempt to understand how the brain works must take into account this huge neuronal diversity. Such diversity is likely the reason why each one of us is unique; even genetically identical twins have different preferences or opinions. But the fundamental mechanisms by which neural stem cells produce such a variety of neuronal types are slowly being revealed.

In contrast to the single mechanism for the production of antibodies (VDJ recombination) in the immune system, several molecular mechanisms contribute to the generation of neuronal diversity (Muotri and Gage 2006). Those mechanisms not only act on the DNA, but also act on the RNA and protein levels, allowing epigenetic modifications to take place. Among these mechanisms, alternative splicing, promoter usage, alternate polyadenylation, RNA editing and post-translation modifications are all part of the genetic tool box present in neuronal precursor cells. However, even such a repertoire is not enough to justify the observed constellation of neuronal types. New mechanisms are likely to be uncovered. We anticipate that novel strategies for the neuronal diversity contribution are hidden in non-coding regions of the genome (Cao et al. 2006; Muotri and Gage 2006). We have recently shown that an engineered human L1 element can retrotranspose in neuronal precursor cells, changing neuron-related gene expression, which, in turn, can influence neuronal cell fate in vitro (Muotri et al. 2005). Moreover, because L1 retrotransposition can also occur in the CNS neuroprogenitor throughout embryo development and in the adult brain of transgenic mice, this unexpected mechanism may contribute to neuronal diversity.

The L1 retrotransposition causes a neuronal genetic mosaicism, i.e., the presence of more than one genetically distinct neuronal type. Such mosaicism might be undetectable unless closely inspected. In fact, genetic mosaicism is frequently overlooked or interpreted as normal variation caused by stochastic developmental factors or the unequal influence of the environment. However, depending on the mosaic nature, frequency, environmental cues, and tissues of origin, even subtle alterations in gene expression can contribute to detectable phenotypic alterations in the organism. Normal processes, such as aging, the generation of immune diversity, and the phenotypic variability between monozygotic twins (such as schizophrenia) can be due to somatic genetic mosaicism (Dipple and McCabe 2000; Machin 1996; Vijg 2000). The stochastic nature of retrotransposon activity, and the large number of genes that this process may affect, could produce an ample spectrum of neuronal diversity, which may affect behavior, cognition and disease risk.

## Silencing and Activation of L1 Retrotransposons

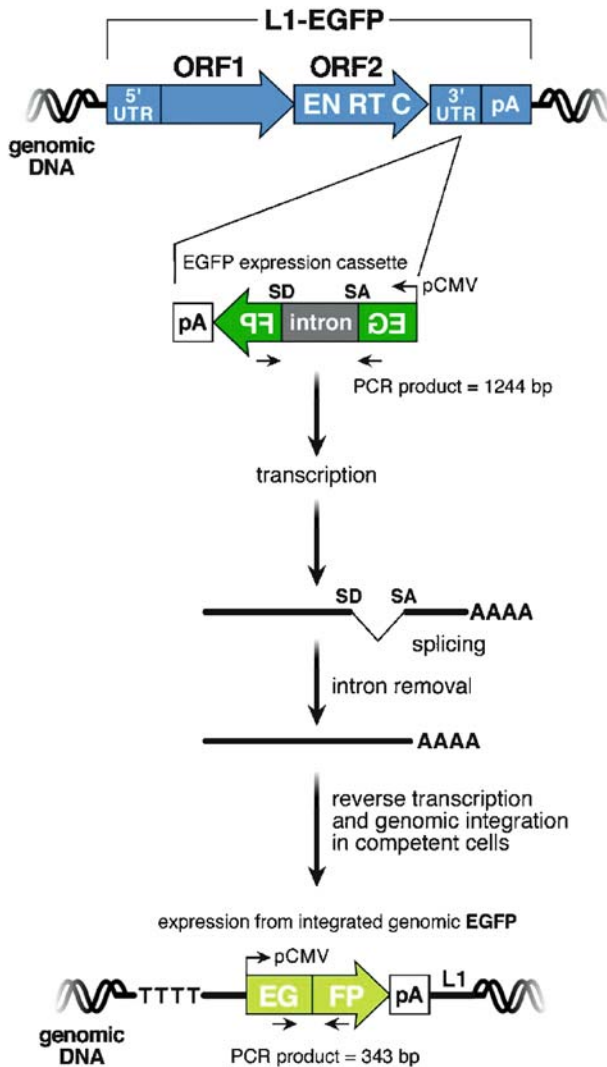
L1 retrotransposons can threaten the structure and regulate the expression of the genome in different ways, such as creating new splicing forms, promoter activation, skipping exons or gene inactivation among others (Gilbert et al. 2005; Kazazian 2004). Such a variety of strategies makes L1 retrotransposons the most creative force shaping the genomes throughout evolution.

Deleterious retrotransposition events in the germ line or in early development have resulted in a variety of genetic disorders, and a somatic L1 retrotransposition in man has resulted in a sporadic case of colon cancer (Kazazian 1998; Miki et al. 1992; Ostertag and Kazazian 2001). In plants and other organisms in which transposition is not restricted to the germ line, somatic activity of transposable elements provides the opportunity for a phenotypic variability that can sometimes be stunning with regard to individual genome flexibility (Lisch 2002). In contrast, retrotransposons are often assumed to be silenced in mammalian somatic tissues. This assumption is based on several arguments. First, there is no detectable level of retrotransposon expression in most somatic tissues. However, only a few tissues have been subjected to meticulous analysis, including subtype cell differences. Second, the somatic silencing of L1s fits well in the “selfish” DNA hypothesis, where the mobile elements exist merely to propagate themselves, so there is no reason to transpose in somatic cells. Finally, there is a clear detection bias of somatic retrotransposition, since only visible mutants, usually leading to human diseases, such as cancer, are detectable (Kazazian 2001; Kazazian et al. 1988). The lack of experimental data and the paucity of natural evidence for somatic L1 retrotransposition have led to the view that L1 activity is restricted to early embryonic and germ line cells, suggesting that intrinsic factors may be present or absent in certain cell types responsible for transposition (Mathias and Scott 1993; Prak et al. 2003). Nonetheless, retrotransposon silencing could be physiologically attenuated. DNA methylation is likely the most effective and global strategy against retrotransposon mobility (Yoder et al. 1997). Accordingly, DNA methyltransferase-1 (*Dmmt1*)-deficient mouse embryos have much higher levels of IAP (Intracisternal A-particle) retrotransposon transcripts than their wild-type littermates (Walsh et al. 1998). Repression of retrotransposition is removed under definite conditions during a specific developmental window. One

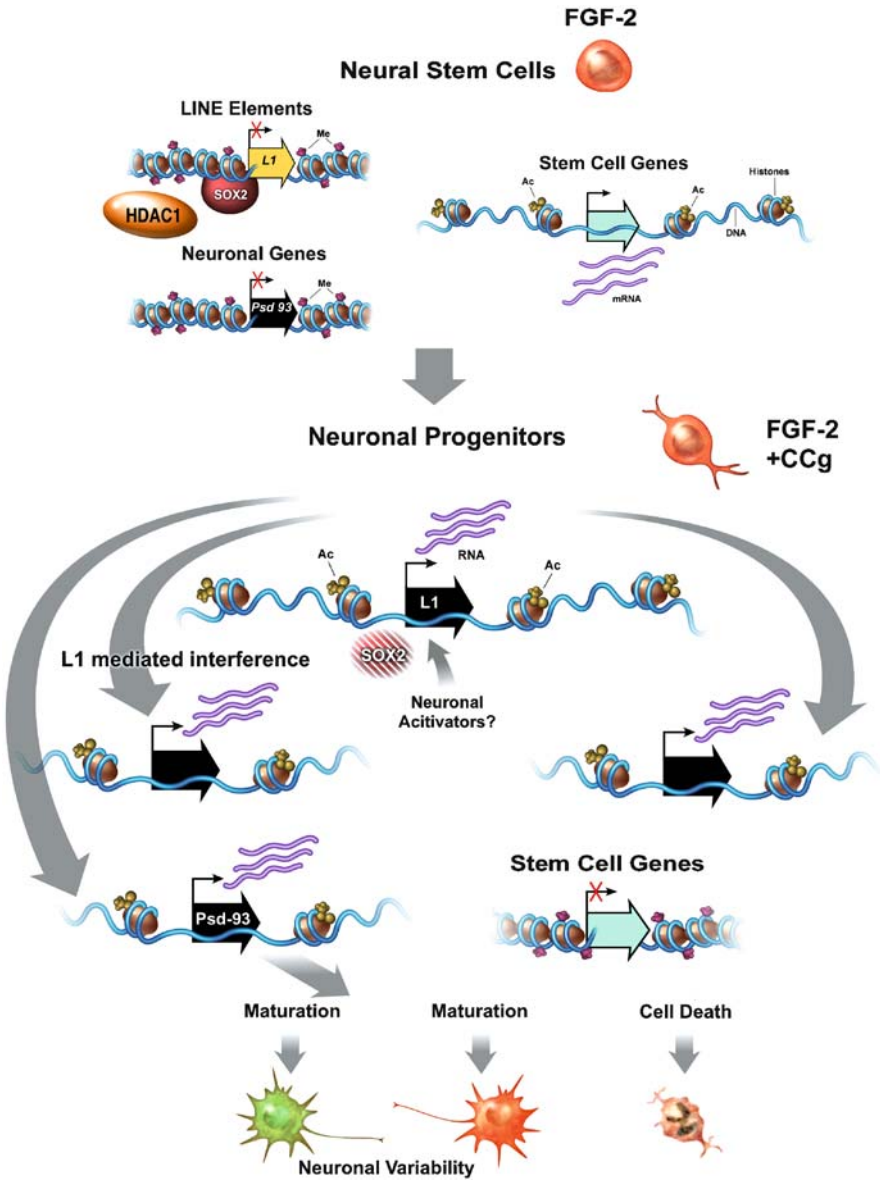
example is the specific induction of IAP elements in the stem cells of the male germ line at undifferentiated stages when they are de-methylated, leading to the hypothesis that a similar mechanism may be found in somatic tissues.

One useful approach to track somatic retrotransposition is the analysis of the L1-EGFP transgenic animal (Muotri et al. 2005; Prak et al. 2003). These mice were engineered to carry an active L1 retrotransposon with an EGFP indicator cassette that only expresses EGFP after retrotransposition and de novo insertions (Fig. 1). Because the assay uses the strong and ubiquitous CMV promoter, it is expected to express EGFP in a large spectrum of somatic cells, if retrotransposition indeed occurs. Obviously, the system will not detect truncated or silenced insertions of the reporter cassette. Of the several somatic tissues analyzed by immunohistochemistry, brain tissue was the only tissue where EGFP expression was detected, specifically in neurons (Muotri et al. 2005). The *in vitro* cellular assay indicated that L1 retrotransposition actually happened in precursor cells rather than postmitotic neurons. Therefore, neuronal precursor cells might have a greater frequency of L1 retrotransposition than other cell types and/or this finding might be due to the long life of neurons, in contrast to the continuous renewal of other cell types. Either way, the presence of EGFP-positive cells indicates that somatic L1 silencing is incomplete in the brain. This observation suggests that L1 retrotransposons might be activated in neuronal precursor cells and the resultant retrotransposition events could alter the expression of neuronal genes. Such a mechanism could, presumably, generate a large spectrum of genetically distinct neurons, adding to the great neuronal variation that is currently observed in the adult CNS. L1 activation is likely regulated by host factors in equilibrium: too much L1 retrotransposition can cause cell damage and induce the cells to die (Haoudi et al. 2004); too little can limit neuronal diversity. The identification of neuronal host factors responsible for L1 repression and/or activation will be extremely important to understanding how retrotransposition is regulated.

L1 expression is dependent on the activation of its own 5'UTR sequence, which acts as a promoter. The human L1 5'UTR is about 1 kb long, harboring one YY1-binding site that is required for proper transcriptional initiation (Athaniar et al. 2004; Swergold 1990), two Sox (sex determining region of Y-chromosome, SRY, related HMG-box) binding sites (Tchenio et al. 2000) and a runt-domain transcription factor 3 (RUNX3) binding site (Yang et al. 2003). Interestingly, none of these factors is germ-cell specific, suggesting the presence of other, unknown factors. Sox proteins are expressed in a variety of tissues, including neural stem cells (NSCs) and testis (Wegner 1999). The lack of Sox2 allowed activation of neuronal genes and differentiation, suggesting that Sox2 may function as a repressor of differentiation in NSCs (Graham et al. 2003). We demonstrated that a decrease in Sox2 expression during the early stages of neuronal differentiation is correlated with an increase in both L1 transcriptional activity and retrotransposition (Muotri et al. 2005). We propose that L1 retrotransposons are silenced in NSCs due to Sox2-mediated transcriptional repression. Down-regulation of Sox2 accompanies chromatin modifications, such as DNA de-methylation and histone acetylation, which may trigger neuronal differentiation (Fig. 2). Such a mechanism preserves genetic stability in NSCs but allows instability to happen in neuronally committed cells.



**Fig. 1.** Detection of L1 retrotransposition in the brains of transgenic mice. The structure of the L1<sub>RP</sub>-EGFP transgene is indicated at the top of the figure. The retrotransposition-competent human L1 (L1<sub>RP</sub>) contains a 5' untranslated region (UTR) that harbors an internal promoter, two open reading frames (ORF1 and ORF2; not drawn to scale), and a 3' UTR that ends in a poly (A) tail. The EGFP retrotransposition indicator cassette consists of a backward copy of the *EGFP* gene whose expression is controlled by the human cytomegalovirus major immediate early promoter (pCMV) and the herpes simplex virus thymidine kinase polyadenylation sequence (pA). This arrangement ensures that EGFP expression will only become activated upon L1 retrotransposition. The *black arrows* indicate PCR primers flanking the intron present in the *EGFP* gene



**Fig. 2.** A model for generation of neuronal diversity by L1 retrotransposition. In neural stem cells, Sox2 expression is correlated with a repression of L1 retrotransposons and neuronal genes. During early phases of neuronal differentiation, there is a reduction in the expression of Sox2 and other neuronal stem cell genes. As a result, L1 transcription can be activated, allowing subsequent retrotransposition into neuronal genes such as for the *Pcd-93* gene. The resulting retrotransposition events can alter gene expression, which, in turn, can influence the phenotype of the resulting cell. The functional variability in gene expression induced by L1 retrotransposition could also contribute, in principle, to the high cell death rate observed in adult neurogenesis, where only a few newly born neurons successfully integrate into the pre-existing neuronal network

## L1 Targets in Neuronal Progenitor Cells

To cause a significant impact on neuronal genomes, new L1 insertions must target important regulatory regions or genes that are being expressed at the moment of neuroblast differentiation. It is likely that only the combination of multiple L1 events, and not an eventual catastrophic insertion in single neurons, will be ultimately responsible for any change in the neuronal network. But L1 retrotransposition is a dangerous situation for the cell, since L1 insertions can hit essential genes that may induce cell death or even target oncogenes, leading to a neoplastic transformation.

Despite the low number of examples, the sequence data from target insertional sites in rat neuroblasts were often close to or inside neuron-associated genes (Muotri et al. 2005). Even with a small sample, two L1 insertions were located in the same gene, indicating that the integration process might not be completely random. Some of these target genes included an olfactory receptor, ion channel-associated genes and a cadherin receptor (Muotri et al. 2005). An L1 insertion in the promoter region of the *Psd-93* gene, encoding a post-synaptic density protein involved in different aspect of synapse formation, significantly increased gene expression level and, consequently, accelerated neuronal maturation in culture. Despite the fact that randomness seems to be the best way for L1 to survive during evolution when they are active in germ cells, somatic insertions might be controlled by local microvariations in DNA chromatin structure that depend on different host factors in specific subsets of cell types. Thus, we propose that L1 insertions in the nervous system are somehow guided to specific gene targets. In a similar way, the yeast Ty1 transposon is highly nonrandom in vivo, being preferentially inserted upstream of tRNA genes (Bachman et al. 2004; Devine and Boeke 1996).

In the L1-EGFP transgenic mice, we followed the retrotransposition of a single human L1 element and retrotransposition was detected by EGFP expression. However, the indicator cassette did not reflect a direct measurement of the 3000 estimated endogenous active L1 retrotransposons (DeBerardinis et al. 1998; Goodier et al. 2001). Moreover, as pointed out before, the L1 retrotransposition assay did not report EGFP-truncated or silenced insertions. Additionally, it certainly did not account for the indirect, in trans, L1-mediated insertions of *Alus*, retrotransposition-defective L1s, and other non-autonomous RNAs. Virtually any RNA molecule can be subject to retrotransposition if hijacked by L1 machinery. Thus, every single developing neuron can potentially carry L1-mediated events, and if part of the resultant insertions occurs in genes expressed during neuronal development, altering gene expression, then it is possible that brain development could be significantly affected by L1 retrotransposition. It has been proposed that stochastic gene expression might be a fundamental part of development and differentiation and, where it is advantageous, these stochastic patterns are retained in the adult organism (Fiering et al. 2000). We speculate that these new L1 retrotransposition events are stably integrated into the genomes of individual neurons during the entire life of the organism. These insertions then act in a stochastic fashion, working as “controlling elements,” fine-tuning to increase the probability that genes will be differentially transcribed. The model is consistent with neuroblast differentiation, in which similar cells are subjected to the same environmental stimuli but do not respond uniformly. Thus, new insertions in neurons represent genomic “scars”



that may have the potential to influence the fate of the resultant cells and, consequently, the function of the neuronal network.

The study of the human L1 5'UTR promoter during neuronal differentiation revealed that L1 activation occurs in the initial stages of cell differentiation. That is exactly the same time that several neuronal genes, such as *NeuroD1*, are upregulated and several cell cycle genes are downregulated (Hsieh et al. 2004; Zhao and Gage 2002). Additionally, the strong anti-mitotic small modulatory NRSE dsRNA, responsible for the neuronal fate of NSCs, is expressed in initial steps of differentiation, activating several NRSE-containing neuron-specific genes and stopping the cell cycle (Kuwabara et al. 2004). These data suggest that there is an orchestrated regulation during neuronal differentiation, avoiding an eventual cell transformation. Such an idea conforms with the low incidence of neuroblastomas (Zhu and Parada 2002) but does not exclude the possibility that an abnormal L1 retrotransposition might lead to a neoplastic transformation in CNS cells.

Taken together, a specific regulation of L1 retrotransposon activity that takes into account its “non-random” neuronal insertion and a specific window of time during cell differentiation may turn a potentially harmful phenomenon into a useful one. The problem now, as with most novel scientific debates, is one of quantification and significance. Future technologies for single-cell endogenous L1 activity assays will bring new insights into the problem. Moreover, the generation of three-dimensional brain mapping depicting the occurrence of L1 retrotransposition will allow the visualization of preferential target neuronal subtypes. The comparison of normal brains with brains where L1 activity is misregulated will provide the structural organization for the design of algorithms that predict eventual retrotransposition-affected neuronal networks or systems.

## Evolutionary Consequences of L1 Impact in Neuronal Genomes

One of the most remarkable findings from the sequencing of the human genome is that retrotransposable elements make up a significant portion of the human DNA (Deininger et al. 2003). Based on reverse transcriptase (RT) phylogeny, L1 elements are most closely related to the group II introns of mitochondria and eubacteria (Cavalier-Smith 1991; Xiong and Eickbush 1990). These studies revealed that the RT enzyme is extremely old and that retroelements can be viewed as relics or molecular fossils of the first primitive replication systems in the progenote. The origin of retroelements possibly traces back to the conversion of RNA-based systems, the “RNA World” (Orgel, 2004), to modern “DNA-based” systems. Current models suggest that these mobile introns of eubacteria were transmitted to eukaryotes during the initial fusion of the eubacterial and archaeobacterial genomes or during the symbiosis that gave rise to the mitochondria, generating the modern-day spliceosomal introns (Zimmerly et al. 1995). Further acquisition of an endonuclease enzyme and a promoter sequence certainly represented important steps in the evolution of L1 retrotransposons, providing autonomy for L1s to insert into many locations throughout the genome.

The apparent lack of obvious function of retroelements in the genome suggests that transposable elements are “selfish DNA,” acting as parasites in the genome to



propagate themselves. This idea has long puzzled scientists and inspired the concept of “junk DNA” to illustrate the idea that such sequences were mere evolutionary remnants (Doolittle and Sapienza 1980; Orgel and Crick 1980). However, the recognition that retrotransposons can actively reshape the genome is slowly challenging this terminology. Moreover, the mammalian genome has suffered waves of transposon bombardment, but the constant, single lineage of L1 history reveals that active L1 were never absent from mammals’ genomes during evolution, suggesting an inextricable link between L1 and their hosts (Furano et al. 2004). The relationship between transposons and their hosts is probably not entirely antagonistic, as several host genes have a high degree of homology to one or more transposable elements. Evidence in the literature points to a somatic function for L1 transcripts, involving cell proliferation (Kuo et al. 1998), differentiation (Mangiacasale et al. 2003) and early embryo development (Pittoggi et al. 2003). Moreover, it is difficult to reconcile why the genome would need so many copies of retrotransposons and whether this expansion has any correlation with retrotransposition itself. The restricted activity of retrotransposons in germ or early embryonic cells apparently fits well with the “selfish DNA” concept, since new insertions will be passed to the next generations, but somatic insertions pose a conundrum. According to the symbiotic theory, it is advantageous to any transposable element to promote host mating, securing the propagation of the “master” elements to the next generations. From this perspective, it is not surprising that advantageous insertional events in the brain, resulting in the better (cultural and social) fitness of the individual organism, also can contribute to the host mating.

The evolution of the CNS provided a notable selective advantage, as information about the environment could be processed rapidly and would allow organisms to more readily meet the challenges of ever-changing environmental conditions. Moreover, epigenetic modification allowed the non-genetic transfer of information or transmission of “culture” at an unprecedented magnitude. Such specialization is highly dependent on the cognitive levels acquired by the species that are directly linked to the complexity of the neuronal network. Therefore, the advantages gained by retaining the mechanisms for somatic retrotransposition may outweigh the cost of a less plastic nervous system. In fact, such a strategy expands the number of functionally distinct neurons that could be produced from a given stem cell gene pool (Muotri and Gage 2006). This characteristic of variety and flexibility may contribute to the uniqueness of an individual brain, even between genetically identical twins. Mobile elements in the brain may be part of the conserved core process responsible for evoking the facilitated, complex, non-random phenotypical variation on which selection may act. It is remarkable to imagine that the brain is a consequence of ancient retrotransposition in eukaryotic cells. Such a possibility has not been considered before, but it was suggested to us by the experimental results.

The identification of L1 elements as potential creative somatic shapers of transcriptional complexity in neuronal genomes may be an important phenomenon for developmental neurosciences. The hypothesis that L1 activity is responsible for “fine-tuning” neuronal wiring waves requires the merger of different fields and may consequently open new ways of considering individual differences and the neuronal correlates of human cognition. Rigorous experimental proof of this model will require attenuation of retrotransposition activity from the mammalian genome and comparing their be-

havior to that of wild type animals. Nonetheless, the experimental approach presents a major methodological challenge for molecular biologists, since a canonical single-gene knockout strategy is no longer suitable. On the other hand, the study of abnormal activation of L1 retrotransposition in the brain may elucidate complex neurological syndromes, permitting an understanding of diseases at a different level.

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