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LINE-1 Retrotransposons in Healthy and Diseased Human Brain

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Abstract

Long interspersed element-1 (LINE-1 or L1) is a transposable element with the ability to self-mobilize throughout the human genome. The L1 elements found in the human brain is hypothesized to date back 56 million years ago and has survived evolution, currently accounting for 17% of the human genome. L1 retrotransposition has been theorized to contribute to somatic mosaicism. This review focuses on the presence of L1 in the healthy and diseased human brain, such as in autism spectrum disorders (ASD). Throughout this exploration, we will discuss the impact L1 has on neurological disorders that can occur throughout the human lifetime. With this, we hope to better understand the complex role of L1 in the human brain development and its implications to human cognition.

Keywords

LINE-1; Retrotransposition; Brain; Neurological Disorders; Autism

Introduction

The invention of the wheel, the landing on the moon, the ability to hypothesize a theory of evolution- is there a single component of the human brain that has allowed us to make all of these great feats? Although the human brain does have slightly larger physical characteristics such as size of cerebral cortex (Hofman 1988; Azevedo et al. 2009; Herculano-Houzel 2009, 2012) and surface area (Hofman 2014) when compared to other species of primates, a new wave of research has started exploring the genetic contribution to the uniqueness of the human brain. The evolution towards the present human brain has been a series of mutations and natural selection. This review will focus on the role of transposable elements, specifically L1 retrotransposons that contributed to this selection and its impact on the human brain, health, and disease throughout a single lifetime. Based on the current data, we postulate that L1 elements can affect the formation of brain networks, leading to alterations in cognition and behavior, such as observed in Autism Spectrum Disorders (ASD) or in late-onset conditions.

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Transposable Elements in the Human Genome

Transposable elements (TEs) are colloquially known as "jumping genes" because of their ability to move, or transpose, within a genome. TEs were first discovered in maize by Barbara McClintock in the 1940s (McClintock 1956). At this time, the idea of mobile DNA was novel and much of the scientific community still believed DNA was stagnant, however, the progression towards the idea of a more dynamic genome has taken precedence and is widely accepted now. TEs are found in all living organisms, but the percentage they occupy within a genome and their ongoing activity vary. In humans specifically, TEs contribute to approximately 45% of the genome (Kazazian 2004).

TEs are categorized into two major classes: DNA transposons and retrotransposons (Goodier and Kazazian 2008). DNA transposons are found to be active in many plants and lower organisms, but the ability to transpose in humans was evolutionarily lost due to mutation. Indeed, DNA transposons only make up about 3% of the human genome (Lander et al. 2001). DNA transposons are often described to replicate through a "cut and paste" mechanism (Munoz-Lopez and Garcia-Perez 2010; Craig 2002). By encoding the enzyme transposase, DNA transposons are removed, or "cut", from one location of the genome and reintegrated, or "pasted" into a new location. Retrotransposons instead work through a "copy and paste" mechanism, which undergoes an RNA intermediate in the process of amplification (Moran and Gilbert 2002). The majority of TEs found in humans and mice are categorized under retrotransposons. Retrotransposons can further be divided by the presence or absence of long terminal repeat sequences (LTR), falling either into the category of LTR or non-LTR retrotransposons respectively. LTR retrotransposons are also known as endogenous retroviruses (ERVs) due to similar structure to simple retroviruses (Rowe and Trono 2011; Maksakova et al. 2008). LTR retrotransposons account for 8% of the human genome (Mager and Stoye 2015), but their activity in our genome is uncertain and is still continuously researched and discussed.

The non-LTR retrotransposons, on the other hand, are known to be active within the human genome (Mills et al. 2007). Non-LTR retrotransposons can further be classified into non-autonomous or autonomous depending if their coding sequence has the enzymatic machinery to mobilize themselves throughout the genome (Lander et al. 2001). Alu and SVA retrotransposons, non-autonomous elements, comprise approximately 10% of the human genome, while long interspersed element-1 (LINE-1 or L1s) are autonomous transposons and contribute to approximately 17% (Mills et al. 2007). L1s are the only known class of autonomous retrotransposons to be active. In 2003, Brouha and colleagues conducted a study where they determined 44% out of 90 L1s with intact open reading frames (ORFs) were polymorphic across the human population. After determining their capability to mobilize through cultured cell assays, termed as retrotransposition, they determined there were six highly active L1s, termed "hot L1s", that comprised 84% of the total retrotransposition capability observed. Five full-length L1s are known to be involved in disease-causing insertions (Divoky et al. 1996; Schwann et al. 1998; Brouha et al. 2002; Dombroski et al. 1991; Holmes et al. 1994). The authors discovered that these five L1s are very active in comparison to the cloned L1s with intact ORFs, suggesting that these hot L1s

are responsible for the retrotransposition occurring in humans, possibly playing a role in predisposition to certain disorders.

Where LINE-1 Elements Impact Humans

The first reported observation of a L1 insertion was in 1988, when Haig Kazazian and colleagues investigated a patient with hemophilia A, who had no familial history of the disorder. Upon investigation, they observed a new exonic L1 insertion in X-linked gene factor VIII, suggesting new L1 insertions in cell types where the next generation can inherit genetic information (i.e. germ cells in early embryogenesis) (Kazazian et al. 1988; Kazazian and Moran 2017; Richardson et al. 2017). Since then, examples of human genetic disorders caused by *de novo* L1 insertions continue to accumulate, and more than 100 cases have been shown to cause heritable diseases, such as haemophilia, β-thalassaemia, Duchenne muscular dystrophy, cystic fibrosis, Apert syndrome, neurofibromatosis and cancer (Belancio et al. 2009; Cordaux and Batzer 2009; Chen et al. 2005). However, recent research has determined that retrotransposition is not only limited to the germline. L1 expression and activity has been observed in several human tumors (Iskow et al. 2010; Lee et al. 2012; Shukla et al. 2013; Solyom et al. 2012) and in selected tissues of the human brain (Baillie et al. 2011; Coufal et al. 2009; Evrony et al. 2012; Muotri et al. 2005; Evrony 2015; Upton et al. 2015) as well, concluding that somatic retrotransposition is more prevalent than previously anticipated. Intriguingly, a new retrotransposition insertion can not only be mutagenic by disrupting a coding sequence. L1 insertions can impact the expression of nearby genes by generating new splice sites, promoters, adenylation signals and transcription factor-binding sites that can reorganize gene expression. L1s can also contribute to genetic instability by generating target site deletions, insertions of flanking DNA, recombination with other retrotransposons, and the possible generation of chromosomal inversions and interchromosomal translocations (Goodier and Kazazian 2008; Beck et al. 2011; Kazazian 2004; Hancks and Kazazian 2012). In addition, inactive L1 elements (unable to mobilize) can contain mutations in their sequence and express truncated proteins causing varying levels of cell toxicity and DNA damage (Kines et al. 2014). In summary, new TE insertions can profoundly affect the human genome in multiple ways, thus this chapter will focus on the association between L1 activity and a complex tissue as the human brain.

In order to understand how L1 elements arrived to the human brain, we must first look at its presence in evolution. During the Eocene, the most ancient subfamilies of L1, HERV, and Alu were hypothesized to first appear in early prosimians, which had relatively small brains when compared to their body mass (Gilbert et al. 2005; Zilles et al. 1989; Linker et al. 2017). About 25 million years ago, additional L1 and Alu subfamilies appeared and SVAs first originated during the split between hominoids and cercopithecoids (Schrago and Russo 2003; Batzer and Deininger 2002; Khan et al. 2006; Wang et al. 2005). Also at this time, the frontal cortex increased in size (Linker et al. 2017). Approximately 5 million years ago, after the Pan-Homo split, the primate brain size dramatically increased (Semendeferi et al. 2002) and in *Homo,* the subfamilies L1Hs, AluYa5, AluYb8, and SVA were the most active, and are still the most active in the human genome today (Cordaux et al. 2006; Ewing and Kazazian 2010; Xing et al. 2009; Linker et al. 2017). Interestingly, human restriction factors have evolved in parallel with transposable elements in order to repress its activity (Castro-

Diaz et al. 2014; Jacobs et al. 2014), however, these elements were still able to escape this repressive mechanism through mutation. Additionally, a study conducted by Ramsay and colleagues (2017) used an induced pluripotent stem cell (iPSC) model to generate RNA-seq data for four different primate species- human, chimpanzee, gorilla, and rhesus. The authors reported 30% of TE instances found in human iPSCs also had orthologous TE instances expressed in chimpanzee and gorilla (Ramsay et al. 2017). Although we have established L1 insertions in the evolution of the primate brain, retrotransposition in somatic cells is a random phenomenon and cannot be evolutionary mapped in the same way. However, these insertions can be studied in different times of a human individual's life. First, we must look to understand the mechanism of how L1 can mobilize within a human.

Retrotransposition Mechanism of Active LINE-1 Elements

As mentioned previously, retrotransposons undergo a copy and paste mechanism in order to reintegrate into new genomic locations. With more than 500,000 L1 copies in the genome (Booth, Ready, & Smith, 1996; Lander et al., 2001), more than 99% are unable to move due to 5' truncation, rearrangement, or mutation (Goodier and Kazazian 2008; Dombroski et al. 1991; Scott et al. 1987; Beck et al. 2010). However, the remaining 80–100 L1s that are mobile are called retrotransposition competent L1s (RC-L1s) (Beck et al. 2010; Brouha et al. 2003). These RC-L1s contain a promoter within its 5' untranslated region (UTR) with sense and antisense activities (Swergold 1990; Speek 2001; Beck et al. 2011; Macia et al. 2011) and ends with a short 3' UTR and a poly(A) tail (Figure 1a) (Dombroski et al. 1991; Scott et al. 1987). RNA can be transcribed and transported into the cytoplasm to encode the open reading frame-1 and open reading frame-2 proteins (ORF1p and ORF2p, respectively) (Moran et al. 1996) (Figure 1b). ORF1 encodes an RNA binding protein with nucleic acid chaperon activity (Hohjoh and Singer 1997b, a; Khazina and Weichenrieder 2009; Martin and Bushman 2001). ORF2 produces a protein with enzymatic activities, two of which include an apurinic/apyrimidinic (AP)- like endonuclease (EN) (Martin et al. 1995; Feng et al. 1996) and a reverse transcriptase (RT) (Mathias et al. 1991). With the exception of the 3' UTR in certain cell types (Moran et al. 1996), all of these components are necessary in RC-L1 mobilization (Figure 1b). More recently, Denli and colleagues (2015) identified an ORF in the human antisense L1 5' UTR. Because of its position before ORF1 and ORF2, it has been named ORF0 (Figure 1a). This primate-specific antisense ORF can be fully encoded by approximately 781 loci in the human genome (Denli et al. 2015; Macia et al. 2017a). Researchers observed an increase in L1 mobility when ORF0 was overexpressed in HEK293T cells and human embryonic stem cell (hESC)-derived neural progenitor cells (NPCs). This suggests that ORF0's ability to enhance L1 activity could contribute to somatic variation (Denli et al. 2015).

Retrotransposition first begins with the generation of a full-length L1 mRNA using the sense internal promoter within its 5' UTR (Figure 1b). The RNA is transported into the cytoplasm where translation occurs to encode ORF1p and ORF2p (Alisch et al. 2006; Dmitriev et al. 2007). Once translated, the L1-encoded proteins bind to the L1-encoding mRNA through a process known as *cis*-preference (Wei et al. 2001). It is believed that this binding forms a ribonucleoprotein particle (RNP) and serves as an essential intermediate throughout the retrotransposition process (Figure 1b) (Doucet et al. 2010; Goodier et al. 2007; Kulpa and

Moran 2005; Martin 1991). The L1-RNP is imported back into the nucleus where a new L1 copy is integrated through target-primed reverse transcription (TPRT) (Luan et al. 1993; Cost et al. 2002). During TPRT, the EN of the L1-ORF2p cleaves the bottom strand of the DNA at a degenerate consensus sequence (5'-TTTT/A-3') (Jurka 1997). With this nick, a 3' OH is exposed (Luan et al. 1993; Cost et al. 2002) and used as a primer for the RT of L1-ORF2p (Monot et al. 2013), where the L1 mRNA serves as a template (Luan et al. 1993) for the generation of cDNA (Figure 1b). The TPRT model may have alternative mechanisms with the possibility of RT activity occurring also in the cytoplasm (Telesnitsky and Goff 1997; Thomas et al. 2017; Garcia Perez and Alarcon-Riquelme 2017). Existing research has shown that the configuration of four T nucleotides at the end of the target DNA is the sequence that will give rise to the highest efficiency of initiation of reverse transcription process (Monot et al. 2013). Although unclear, a process similar to the one just described occurs with the top strand of DNA, generating yet another L1 insertion in the genome. While it seems as though many L1 insertions are produced, the majority are 5' truncated (Grimaldi et al. 1984; Goodier and Kazazian 2008). This truncation prevents the formation of a functional RNP intermediate and is therefore incapable of mobilization. Although L1s are major drivers of genome evolution, these L1-driven mutagenic events can also cause genetic disorders, thus host restriction mechanisms that control the accumulation of new insertions are essential on the stability of mammalian genomes.

Regulation of L1 activity in the mammalian genome

The L1 retrotransposition cycle as described is very complex and entails many crucial steps, however, mammalian evolution has tried to prevent the occurrence of retrotransposition at different points of the cycle. Methylation is one host factor that can inhibit L1 expression. L1 promoters include a CpG island which has the possibility of being methylated, consequently inhibiting expression (Coufal et al. 2009; Bourc'his and Bestor 2004; Thayer et al. 1993). DNA methyltransferase-3 like (DNMT3L) plays a role in DNA-methylation of certain retroelements in primordial germ cells (Bourc'his and Bestor 2004; Macia et al. 2015). The early embryogenesis stage is associated with hypomethylation, possibly relating to the accumulation of L1 copies during this period (Munoz-Lopez et al. 2011). This hypomethylation of L1 promoters serves as a characteristic of mouse, human embryonic stem cells (hESCs) and induced pluripotent stem cells (hiPSCs) (Garcia-Perez et al. 2007; Munoz-Lopez et al. 2011; Shen et al. 2006; Wissing et al. 2012; Macia et al. 2011). Further along in the L1 retrotransposition cycle, splicing has been shown to regulate L1 mobilization in somatic tissues and cell cultures by generating non-functional LINE-1 transcripts (Belancio et al., 2006; Perepelitsa-Belancio and Deininger, 2003). In addition, PIWI proteins, which are highly conserved, interact with PIWI-interacting small RNAs (piRNAs) for TE RNA degradation (Heras et al. 2014). piRNAs are predicted to work in unison with DNA methylation, with the piRNA pathway generating DNA methylation patterns on repeated elements in mice (Aravin et al. 2007; Aravin et al. 2008; Newkirk et al. 2017; Heras et al. 2014; Xiol et al. 2014; Brennecke et al. 2007). Also, the Microprocessor (Drosha-DGCR8), which is required for microRNA biogenesis, has been shown to also regulate L1 mRNAs (Heras et al. 2013). Finally, post-translational control mechanisms have been proposed to restrict the ability of L1 to mobilize. Host factors like ribonuclease L

(RNaseL), described to degrade L1 RNA produced by the sense and antisense L1 promoters (Yang and Kazazian 2006; Zhang et al. 2014); TEX19.1, which can directly interact with the L1-ORF1p in mouse embryonic stem cells, stimulating its degradation (MacLennan et al. 2017); APOBEC3 (A3), a cytidine deaminase enzyme, capable of limiting L1 retrotransposition through deaminating and editing L1 sequences (Schumann 2007; Wissing et al. 2011; Marchetto et al. 2013; Richardson et al. 2014b), are a few examples shown to interfere with later steps of the retrotransposition cycle. The majority of host factors that control L1 retrotransposition is yet to be discovered, however research in this area continues in order to better understand the mechanisms of regulation and the coevolution with humans. L1 retrotransposition can impact the developing human brain at different stages of human life (infancy, childhood, adulthood, aging) in health and disease (McConnell et al. 2017).

L1, brain and disease

L1 mobilization is active in healthy human brain (Muotri et al. 2005; Coufal et al. 2009; Baillie et al. 2011; Evrony et al. 2012; Goodier 2014). Indeed, several studies in healthy post-mortem brains and hESC-derived neural cells have provided evidence of accumulation of L1 insertions. There is currently an array of techniques in the field to detect L1 expression in neuronal lineage. The first method, used by Moran and colleagues (1996), utilized an active engineered L1 element tagged with a reporter cassette that was only activated after a complete round of retrotransposition. Since then, retrotransposition assays have often been used as a reliable method to detect L1 retrotransposition (Garcia-Perez et al. 2007, 2010; Wissing et al. 2011). A cell culture-based retrotransposition assay consists of a complete human RC-L1 tagged with a reporter cassette containing an antisense copy of a specific marker, which is disrupted by an intron. The RC-L1 and the intron are in the same transcriptional orientation, but the reporter cassette is in the opposite transcriptional orientation (Moran et al. 1996). The reporter gene is flanked by a heterologous promoter and a polyadenylation signal. This arrangement allows L1 transcripts to splice the intron, and due to the antisense orientation, expression of the marker can only be detected when the transcript is reverse transcribed, integrated, and expressed by the heterologous promoter (Moran et al. 1996). The different reporter cassettes used in the detection of L1 mobilization are diverse, from fluorescent protein, luciferase or antibiotic selection genes. For example, L1-EGFP (enhanced green fluorescent protein) indicator cassettes have also been used to visually detect L1 retrotransposition through EGFP-positive cells in adult rat and human NPCs (Muotri et al. 2005), hESCs (Garcia-Perez et al. 2007) and in transgenic L1-EGFP mice (Muotri et al. 2005), where the EGFP-positive cells are only seen after L1 retrotransposition is completed. In 2009, Coufal and colleagues isolated NPCs from human fetal brain stem cells and additionally derived NPCs from hESCs. Using these two cell types, the authors performed retrotransposition assays and detected L1 retrotransposition events in both conditions (Coufal et al. 2009). Furthermore, through quantitative polymerase chain reaction (qPCR), the authors observed a significantly higher amount of L1 ORF2 copy number in various regions of healthy adult human brain sample when compared to the liver and heart, indeed suggesting more L1 activity in the brain. Notably, Coufal and colleagues consistently noticed higher levels of L1 ORF2 copy number in the adult hippocampus when compared to other regions of the brain, providing evidence that L1 elements could be active

as early as the formation of the central nervous system. Although the specific L1 integration sites within the genome cannot be accurately determined (Kempen et al. 2017), the striking difference between the hippocampus and other areas of the brain and body demonstrates the contribution L1 has in neuronal diversity and in somatic mosaicism in general (Coufal et al. 2009; Richardson et al. 2014a). In 2017, Macia and colleagues explored L1's ability to retrotranspose in somatic cells as mesenchymal stem cells (MSCs), hematopoietic stem cells (HSCs) and NPCs, as well as in mature human neuronal cells. The authors were able to detect higher levels of L1 mRNA and L1 ORF1p in NPCs when compared to other somatic cells (Macia et al. 2017b; Garcia-Perez et al. 2016). The majority of the cells in the human brain are mature neuronal cells (Tang et al. 2001). Thus, the researchers then focused on L1 retrotransposition in mature nondividing cells. In order to do this, a plasmid containing an RC-L1 (Brouha et al. 2002) was transfected into differentiating NPCs at day 31(Macia and Muotri 2017), showing efficient L1 retrotransposition in these nondividing mature neuronal cells (Macia et al. 2017b). Although these L1-fluorescent reporter assays are convenient, Kempen and colleagues (2017) point out that the fairly large EGFP cassette must be reverse transcribed for fluorescence to ensue, making this method variable. Additionally, there is also the possibility of the EGFP promoter being silenced by the host genome (Garcia-Perez et al, 2010). Also, the use of retrotransposition assays in this field does not necessarily conclude that endogenous elements retrotranspose in the cell type or tissue, rather it allows researchers to determine if a particular cell type or tissue can support retrotransposition.

More recently, to subdue these disadvantages, studies have been utilizing high-throughput DNA sequencing to both detect and locate endogenous L1 variants, providing stronger evidence of L1's role in somatic mosaicism. In 2011, Baillie and colleagues described a high-throughput method, named RC-seq, in order to detect L1 insertions in hippocampal and caudate nucleus samples of three healthy individuals. With the use of RC-seq, the authors identified somatic L1 insertions within protein-coding genes differentially expressed and active in the brain (Baillie et al. 2011). Researchers validated only a portion of their somatic candidate insertions using 5' end nested PCR. Out of their 850 found full-length L1 insertions, they selected 14 L1 examples to validate, and all were confirmed. In 2012, Evrony and colleagues used single-neuron genome-wide sequencing to detect full-length L1 insertions. 300 single neurons originating from the cerebral cortex and caudate nucleus of three normal individuals were profiled, and although somatic L1 insertions were observed, only about 1.1 somatic insertions were found per neuron, and less than 0.6 unique somatic insertions were discovered per neuron. These results contradict the Coufal et al. (2009) study and instead suggest L1 does not contribute to neuronal diversity between the cortex and caudate (Evrony et al. 2012). However, out of the 81 insertions found, only five were validated. On the other hand, in 2015, Upton and colleagues utilized RC-seq for single cell analysis of hippocampal neuron and glial cell. The authors estimated 13.7 and 6.5 somatic L1 insertions in each cell type respectively (Upton et al. 2015), which displays a drastically different result from Evrony et al. (2012). Upon further investigation of the hippocampal L1 insertions, the authors observed enrichment in transcribed neuronal stem cell enhancers and hippocampus genes, suggesting retrotransposition in the brain and diversity of genomes between individual neurons (Upton et al. 2015). However, again validation of the L1 insertions was limited. In 2016, Erwin and colleagues performed single-cell and bulk

sequencing methods to capture Somatic L1 Associated Variants (SLAVs) in frontal cortex and hippocampus samples from three healthy individuals. Single nuclei were isolated and amplified by multiple displacement amplification (MDA). Similar to Upton et al. (2015), the results of this study are in favor of L1 as a contributor to somatic mosaicism. In order to isolate somatic insertions from false positives, the authors did not take into account previously identified known non-reference germline loci and private germline insertion loci. Whole genome amplification often occurs near known L1 loci (Evrony et al. 2012; Upton et al. 2015), and the machine-learning approach used cannot detect proximity to know L1 loci, therefore the researchers did not consider candidates within 10 kb of known non-reference germline loci, germline L1HS, and PA2 and PA3, both of which are subfamilies of L1s. Chimeric DNA rearrangements, often generated when utilizing MDA (Zhang et al. 2006), have been shown infrequent for segments more than 10 kb apart, however SLAVs are still difficult to differentiate from a MDA chimera unless found and validated in more than one MDA amplified cell or in bulk (Lasken and Stockwell 2007). Indeed, confirmation of somatic L1 retrotransposition was found in neurons, glia, and progenitor cells and was extensively validated through PCR and Sanger sequencing. For validation, the authors used a PCR assay confirming the 3' end of the L1 candidate using complementary primers to both the 3' end of L1 and the flanking genomic sequence. They also performed another PCR assay using primers complementary to the 5' and 3' flanking sequences. This was important for validation because chimera formation often occurs when a displaced 3' end primes to new templates (Lasken and Stockwell 2007). SLAVs not containing target site duplications were found and deemed somatic deletions that were independent of retrotransposition. The authors hypothesized for these SLAVs to occur primarily at germline cells. By overexpressing L1 in human hippocampal neural differentiation, researchers confirmed an increase in dsDNA damage at genomic L1 loci suggesting these genomic regions to be predisposed to somatic copy number variants (CNVs) in the brain and thus a heritable genetic contributor to somatic mosaicism (Erwin et al. 2016). Additionally, recent studies have suggested that some polymorphic L1 copies (Philippe et al. 2016) and some Alu elements (Payer et al. 2017) within individuals might be associated with an increased risk to certain human disorders. Although somatic mutations are not inherited, donor L1s, which cause *de novo* L1 insertions within somatic cells, can be passed through the germline and be a source of both germline and somatic mosaicism (Faulkner and Garcia-Perez 2017; Richardson et al. 2017; Scott et al. 2016). It has been shown that active donor L1s in somatic cells have the capability of predisposing an individual to specific diseases and cancers (Scott et al. 2016; Singer et al. 2010; Miki et al. 1992), but this is dependent on their region of mobilization (Brouha et al. 2003; Evrony 2015; Faulkner and Garcia-Perez 2017). In 2016, Carreira and colleagues utilized RC-seq and investigated L1 mutations in 14 glioblastoma multiforme (GBM) tumors. In four of these tumors, the authors discovered an endonuclease-independent polymorphic L1 insertion, two L1-associated rearrangements and an Alu-Alu recombination event in close proximity to an L1, however after sequencing the L1 integration sites, there was no found tumor-specific, endonuclease-dependent L1 insertions (Carreira et al. 2016). In sum, the study of L1 activity with new technologies has allowed us to find L1 activity in the healthy brain, but is also well studied among brain disorders that span throughout a human's lifetime.

1- The human infant brain

L1 and Aicardi-Goutieres Syndrome—Aicardi-Goutieres Syndrome (AGS) is a severe neuroinflammatory disorder that is inherited in an autosomal recessive pattern with an onset in early infancy (Crow et al. 2015) (Figure 2). AGS often arises when three-prime repair exonuclease 1 (TREX1) becomes mutated (Crow and Manel 2015). TREX1 is an anti-viral DNase that breaks down nucleic acids in the cytosol (Mazur and Perrino 1999; Richards et al. 2007). With this function, TREX1 prevents accumulation of single-stranded and double stranded DNA, in turn preventing type I interferon (IFN) associated inflammatory response (Crow and Rehwinkel 2009; Yang et al. 2007). With TREX1 function compromised, abnormal amounts of nucleic acid species in the cytosol can result in an unintended immune response.

In 2008, Stetson and colleagues were the first to recognize the relationship between TREX1 and L1 retrotransposons (Stetson et al. 2008). Curious about the source of the TREX1 DNA substrates that activate the interferon-stimulatory DNA (ISD) pathway, researchers purified, amplified, and cloned the endogenous TREX1 DNA substrates from TREX-1 knock out (KO) mice. They then compared the DNA recovered from control and TREX1-deficient mice hearts. The DNA collected from TREX1-deficient hearts was more abundant (32-fold increase), suggesting the KO heart extracts had substantially more DNA that the wild-type (WT) extracts. Additionally, DNA fragments derived from endogenous retroelements were highly detected in the deficient hearts when compared to wild-type. The authors recovered 25 retroelement sequences (consisting of LINE, LTR, and short interspersed elements (SINE)) from knockout samples, 12 of which were derived from L1 retrotransposons. Mapping between the ssDNA fragments to consensus L1 sequences showed that L1-derived DNA fragments mapped preferentially to the 3' end of the consensus sequence, alluding to the majority of L1 copies that are 5' truncated. The authors also analyzed L1 retrotransposition by co-transfecting an engineered active L1 element containing a neomycin resistance cassette (*neo^r*) in reverse orientation to the retroviral coding sequence, with and without a TREX1 expression vector. They used a human L1 element and a LTR-containing murine intracisternal type A particle (IAP) as their marked retroelements. When the marked element was transcribed into mRNA, reverse transcribed, and integrated into the genome, the *neo^r* gene became active. As a control, HeLa cells were transfected with IAP and formed neomycin-resistant colonies, with each colony representing a single retrotransposition event. The authors observed a reduction in IAP retrotransposition efficiency when they co-transfected with a TREX1 expression vector. An 80% reduction in L1 retrotransposition was also seen with an expression vector for TREX1. Lastly, the authors also focused on AGS-causing TREX1 mutations and their effect on IAP and L1 retrotransposition. Loss of function is observed in TREX1 R114H and TREX1 V201D mutations. The mutations, both which cause recessive AGS, did not affect IAP or L1 retrotransposition. When the TREX1 D200N catalytic mutant, which causes autosomal dominant AGS, was co-transfected, an increase in IAP retrotransposition efficiency was observed, but not for L1 retrotransposition. This was the first suggestion that DNA fragments derived from endogenous retroelements accumulate in TREX1-deficient samples.

A study conducted by Pokatayev and colleagues (2016) modeled AGS in mice by exploring the associated RNase H2 mutation. RNase H2 is the main contributor to ribonuclease H activity. It plays a role in removing ribonucleotides accidentally incorporated by DNA polymerases within DNA-DNA duplexes (Nick McElhinny et al. 2010; Reijns et al. 2012; Chon et al. 2013). A mutation in the catalytic A subunit results in a more severe disease phenotype when compared to the other subunits. In the presence of a mutation in the conserved glycine (G37S) on the RNase H2A subunit, an early onset of AGS occurs (Crow et al. 2006). When Glycine 37 is substituted with Serine in RNase H2, a reduction in RNase activity is observed (Rohman et al. 2008; Chon et al. 2009; Crow et al. 2006; Coffin et al. 2011). Researchers produced a mouse model that reflected AGS patients by knocking in both RNase H2 copies with G37S mutation, resulting in homozygous Rnaseh2a$^{G37s/G37s}$ mice, causing interferon stimulated gene (ISG) activation. Through measurement of ISG expression levels in mutated and control embryos, researchers determined the G37S mutation activates a DNA-sensing cGAS-STING pathway. When the protein cyclic GMP-AMP Synthase (cGAS) detects cytosolic DNA, it produces cGAMP leading to activation of the STING pathway. Additionally, the authors measured L1 DNA levels in the mice from cytosolic extract. They observed high levels of L1 DNA in the G37S-deficient embryos suggesting this mutation increases L1 DNA and consequently activates the cGAS-STING pathway.

Recently, Thomas and colleagues (2017) also investigated the relationship between L1 elements and type I IFN inflammation, but rather, in a human developmental model. Using the CRIPSR/Cas9 genome-editing system, authors generated three different cell lines, each with a distinct *TREX1* mutation, and differentiated each cell line into NPCs, neurons, cortical organoids, and astrocytes. The authors also utilized two reverse-transcriptase inhibitors (RTis): Lamivudine (3TC) and Stavudine (d4T) that have been previously shown to inhibit L1 retrotransposition (Dai et al. 2011). Researchers extracted and sequenced extrachromosomal DNA from a TREX-1 deficient NPC line, its isogenic control, and the TREX-1 deficient line treated with 3TC/d4T. After sequencing, the authors detected an abundant amount of repetitive elements, more so, the TREX-1 deficient line contained an increase in L1 elements when compared to control. Particularly, the TREX-1 deficient line contained 70% more human-specific L1 (L1 Hs) when compared to control, but with 3TC/d4T treatment, the L1 and L1 Hs levels returned to near normal. Throughout the neuronal differentiation process of the TREX1-deficient lines, the authors observed a morphology relating to cell sickness and a downregulation of canonical neuronal markers not seen in control lines. By measuring an increase in cleaved caspase-3 (CC3) and terminal deoxynucleotidyl transferase dUTP nick end labeling (TUNEL)-positive cells, they determined the TREX1-deficient cells were experiencing neurotoxicity. 3TC/d4T treated neurons and organoids revealed a healthier appearance with lower CC3 and TUNEL-positive cells, suggesting the RTis rescued neurotoxicity. Similarly, the 3TC/d4T treatment also reduced expression of *IFN*b and *IFNa*13 levels in TREX-1 deficient astrocytes to near control, suggesting that L1 retroelements contribute a significant amount to intracellular DNA species and consequently stimulate type I IFN expression. Treatment with 3TC/d4T also reduced phosphorylated IRF3 levels to control and reduced three out of the six STING-dependent ISGS that were upregulated in TREX1-deficient astrocytes. Ultimately, these data

propose IRF3 activation from cytosolic DNA induces both type I IFN and ISG upregulation in TREX1-deficient astrocytes.

AGS is also associated with SAMHD1 mutations (Dale et al. 2010; Rice et al. 2009; Thiele et al. 2010; Xin et al. 2011). SAMHD1 is a known inhibitor against certain retroviruses, including HIV and simian immunodeficiency virus (SIV) (Hrecka et al. 2011; Laguette et al. 2011). In 2013, Zhao and colleagues demonstrated that the SAMHD1 protein inhibits L1 retrotransposition using an L1-EGFP reporter assay in HEK293T cells. While examining AGS patients with SAMHD1 mutations, the authors observed a significant reduction of L1 inhibition in these individuals (Zhao et al. 2013). The researchers suggest that nuclear localization is necessary for SAMHD1-mediated L1 inhibition because the nucleus is where both L1 reverse transcription occurs and SAMHD1 localizes (Zhao et al. 2013). Through the use of qPCR and a L1 element amplification protocol (LEAP) assay, which assesses L1 ORF2p's ability to reverse transcribe L1 RNA in vitro (Kopera et al. 2016; Kulpa and Moran 2006), the authors determined that SAMHD1 reduced ORF2p expression and ORF2-mediated endogenous reverse transcription of L1 RNA by 62% and 83%, respectively (Zhao et al. 2013). This provides evidence identifying L1 ORF2p and its reverse transcriptase as a target of SAMHD1.

L1 and Ataxia-Telangiectasia—Ataxia-telangiectasia (AT) is a progressive neurodegenerative disease with an onset between the ages of one and four, and a life expectancy typically into early adulthood (Gatti and Perlman 1993) (Figure 2). AT is caused by mutation in the *ataxia telangiectasia mutated (ATM)* gene, which encodes a serine/threonine kinase that is activated by double-stranded DNA breaks and senses cellular DNA damage (Shiloh 2001). Upon activation, DNA damage checkpoint and cell cycle arrest occurs. The DNA is either repaired or p53-mediated apoptosis ensues for the cell (Shiloh 2001). In 2011, Coufal and colleagues investigated the relationship between L1 retrotransposition and ATM deficiency using four different approaches: a mouse model, an embryonic/neuronal stem cell model, a cancer cell line model, and an examination of postmortem human brain tissue (Coufal et al. 2011). Researchers generated *ATM* KO mice containing an L1-EGFP transgene and observed an increase in the number of EGFP-positive cells in *ATM* KO mice when compared to controls, suggesting the *ATM* KO mice have an increase in retrotransposition events. The most striking increase was seen in the hippocampus. Thereafter, hESC-derived NPCs were generated with shRNAs knocking down ATM expression and subsequently reducing protein levels. Researchers observed a twofold increase in L1 retrotransposition in ATM-deficient NPCs. Turning to a parental human HCT116 colorectal cancer cell line and its isogenic derivatives that lacked the *p53* gene or genes necessary for nonhomologous end-joining (NHEJ), the authors explored the role of ATM in L1 mobilization in a non-embryonic/non-neuronal cell type. They observed L1 retrotransposition in both p53-proficient and –deficient HCT116 cells, but reported a twofold increase in ATM knockdown p53-deficient HCT116 cells. Lastly, authors used qPCR to analyze the copy number of endogenous, human specific L1s in hippocampal sections from AT patients. An increase in ORF2 copy numbers in AT neurons was observed when compared to age- and sex-matched control patients, thereby again suggesting an increase in L1 retrotransposition in AT patients.

In all, these studies have highlighted disorders that show the impact L1 insertions have on the human infant brain, nevertheless the adult brain is still susceptible to L1-associated brain disorders.

L1, Autism and Rett Syndrome—Autism and the autism spectrum disorders (ASD) are the most severe developmental disabilities prevalent in today's society (American Psychological Association, 2017). Affecting 1 in 68 children (Center for Disease Control, 2017), ASD affects all racial, ethnic, and socioeconomic groups. According to the fifth edition of the *Diagnostic and Statistical Manual of Mental Disorders,* ASD is characterized by two main symptoms: deficits in both verbal and nonverbal social communication and repetitive behaviors. Criteria for diagnosis states that these symptoms must have occurred early in development and are measured in severity by the amount of support the individual needs. Autism, along with other early onset childhood neurological disorders, have been the focus of research and discussion within the scientific community (Figure 2).

The genesis of ASD still remains unknown, although studies suggests that autism develops from a combination of genetic and non-genetic, or environmental influences (Grabrucker 2012). Phenotypic characteristics of ASD are often shown to be heritable through family and twin studies (Sandin et al. 2014; Hallmayer et al. 2011; Folstein and Rutter 1977; Bailey et al. 1995; Ronald and Hoekstra 2011). With these genetic implications, genome-wide analyses have become popular in this research field to determine genetic variants. Among the genetic variants found, the most noteworthy discovery is the identification of protein-disrupting *de novo* copy-number variants (CNVs) (Szatmari et al. 2007; Sebat et al. 2007; Ronald and Hoekstra 2011; Pinto et al. 2010; Marshall et al. 2008; Levy et al. 2011; Itsara et al. 2010; Glessner et al. 2009; Bucan et al. 2009). The genetic variants were only detected in the affected child, not in the healthy parents, suggesting their appearance occurred in the germline. The most recognized CNVs in autism research are 16p11.2 deletions and 15q11-q13 duplications (Sanders et al. 2015). A recent study conducted in China performed a genome-wide CNV analysis in 546 subjects (343 parent and child trios) with ASD (Guo et al. 2017). Existing genome-wide studies have mainly occurred in primary European samples, making this particular study novel. In all, they detected an overall higher number of CNVs in patients with ASD when compared to controls. They confirmed the reoccurrence of the 15q11-13 *de novo* duplication CNV among their subjects and actually reported a higher frequency of occurrence when compared to primary European samples. Another study analyzed 5,193 individuals, 2,620 of those individuals were diagnosed with ASD, and the remaining were relatives (RK et al. 2017). The study identified 61 ASD risk-genes, reporting 54 *de novo* loss-of-function (LOF) mutations/missense mutations and seven maternally inherited LOF mutations, including *MECP2, AFF2, and PCDH11X*. In total, approximately 4% of the study's subjects carried these identified mutations. 43 out of the 61 ASD risk-genes mentioned have previously been detected in earlier CNV studies. With CNVs possibly leading to the development of sporadic disorders including ASD, research has also focused on what contributes to CNV instability. Intriguingly, transposable elements have been associated with this. One source of CNVs is non-allelic homologous recombination (NAHR) between low-copy repeat (LCR) genome sequences (Stankiewicz and Lupski 2002). High-copy repeats, which contribute to a larger portion of the human genome when compared to

LCRs, can also contribute to CNV instability. Among high-copy repeats are interspersed repeats, which make up 44% of the human genome (Lander et al. 2001). Existing research has shown these transposable elements to be associated with supporting NAHR and the formation of CNVs (Sasaki et al. 2010; Matejas et al. 2006; Gu et al. 2008; Erez et al. 2009; de Smith et al. 2008). Indeed, L1 retrotransposons in particular, have been associated with the autism spectrum disorders (Muotri et al. 2010; Shpyleva et al. 2017).

Rett syndrome (RTT), once considered a part of the ASD, is a progressive neurological disorder associated with the mutation of the X-linked gene methyl CpG binding protein 2 (MeCP2) (Amir et al. 1999). MeCP2 epigenetically regulates its target genes by binding to methylated CpG dinucleotides within promoters, acting as a transcriptional repressor (Chahrour et al. 2008; Yasui et al. 2007). L1 5' UTR sequences are included among MeCP2 targets resulting in methylation-dependent repression (Yu et al. 2001; Klose et al. 2005; Muotri et al. 2010). RTT patients seem to have normal development until 6–18 months of age (Figure 2), however it is followed by impaired motor function, regression of developmental skills, and autistic characteristics and behaviors (Neul et al. 2010). Muotri and colleagues (2010) showed MeCP2 regulation of L1 expression and retrotransposition in mouse and human samples. Muotri et al. compared wild-type and MeCP2 KO brains of L1-EGFP transgenic mice and observed a higher number of EGFP-positive cells in the MeCP2 KO mice brains when compared to wild-type, suggesting an increase in retrotransposition events in the KO mice. Similarly, a two-fold increase of EGFP-positive cells were observed in RTT NPCs in comparison to controls, suggesting the LOF mutation of MeCP2 (as in RTT patients) correlates with an accumulation of L1 insertions. L1 ORF2 sequences in human brain were also analyzed using qPCR. The brains of RTT patients showed a significantly higher number of ORF2 sequences when compared to age- and gender-matched controls. Thus, for the first time, investigators showed that disease-related genetic mutations could influence the frequency of neuronal L1 retrotransposition.

Another study recently examined the levels of L1 ORF1 and ORF2 transcripts in idiopathic autism postmortem brain, looking at four brain regions: BA9 (frontal cortex), BA24 (anterior cingulate), BA22 (auditory processing), and cerebellum (Shpyleva et al. 2017). In this study, Sphyleva and colleagues observed a significant increase in total ORF1 and ORF2 RNA and mRNA in the autism cerebellum compared to control, however there was no significant difference in overall L1 copies. Correspondingly to Muotri et al., the authors used chromatin immunoprecipitation (ChIP) technology to measure MeCP2 binding to the 5' promoter region. Although no significant difference of binding was observed between autism and control samples, authors detected a negative association between MeCP2 binding to 5' UTR and ORF1 expression in autism brains not found in control, proposing that reduced MeCP2 binding contributes to the increase in ORF1 expression seen in the autism cerebellum. To investigate L1 expression in the presence of epigenetic alterations, researchers used methylated DNA immunoprecipitation (MeDIP) methodology. They reported no differences in DNA methylation density in 5' UTR, ORF1, and ORF2 sequences between autism and control samples, however, trimethylation of histone H3 lysine 9 (H3K9me3), which prevents L1 activation, was significantly reduced at ORF1 and ORF2 sequences. This suggests that reduced H3K9me3 levels, and consequently an increase in chromatin accessibility, contributes to the overexpression of ORF1 and ORF2 in the autism cerebellum. Thus, it is

intriguing that L1 expression might be upregulated in a fraction of the ASD brain, generating local mosaicism upon retrotransposition. Future work will focus on the mapping of neurons and circuits that could be affected by this mechanism. It is tempting to propose that the L1 mosaicism in early development could affect certain brain regions but not others, contributing to the heterogeneity of the ASD behavior later in life, including some of the "savant" skills observed in certain individuals with ASD.

2- The young adult brain

L1 and Schizophrenia—According to the *Diagnostic and Statistical Manual of Mental Disorders,* schizophrenia is the most common psychosis with symptoms including hallucinations, delusions, disorganized thinking, abnormal motor behavior, and negative symptoms. Symptoms typically develop in early adulthood (Figure 2). Schizophrenia is considered a neuropsychiatric disorder associated with both genetic and environmental factors (Keshavan et al. 2011). Many schizophrenia studies performed have created a strong association between microdeletions in chromosome 22q11.2 and schizophrenia (Karayiorgou et al. 1995; Xu et al. 2008). The 22q11.2 deletion syndrome has an incidence of 1 in 2000–4000 live births (Robin and Shprintzen 2005; Kobrynski and Sullivan 2007; Botto et al. 2003). Children with this phenotype have consistently revealed language delays (Moss et al. 1999; Gerdes et al. 1999; Scherer et al. 1999; Solot et al. 2000; Solot et al. 2001) and impairments in attention and executive function (Woodin et al. 2001; Sobin et al. 2004). Also, verbal memory is constantly reported stronger than visual-spatial memory (Bearden et al. 2001; Lajiness-O'Neill et al. 2005; Sobin et al. 2005). These individuals are typically diagnosed first with attention-deficit hyperactivity disorder (ADHD), generalized anxiety disorder, obsessive-compulsive disorder or ASD (Arnold et al. 2001; Feinstein et al. 2002; Antshel et al. 2006; Antshel et al. 2007; Vorstman et al. 2006). By early adulthood, up to one-third of these individuals develop schizophrenia or schizoaffective disorder (Pulver et al. 1994; Murphy et al. 1999; Gothelf et al. 2007; Green et al. 2009). The 22q11.2 deletion accounts for 1–2% of schizophrenia cases and is a recurrent structural mutation responsible for sporadic cases of schizophrenia (Karayiorgou et al. 1995; Xu et al. 2008; Consortium 2008; Stefansson et al. 2008). In a recent study, Guffanti and colleagues sequenced a family of six using next generation sequencing. Out of the six family members, four are affected (the mother and three children). The authors identified many non-reference L1s, which are L1s that are either present or absent in individuals and are not annotated in the current release of the genome (Guffanti et al. 2016). More than one third of the non-reference L1s detected were located in the open reading frame of protein-coding genes implicated in schizophrenia (Guffanti et al. 2016), suggesting that L1 retrotransposition contributes to the pathogenesis of schizophrenia.

In 2014, Bundo and colleagues observed a high L1 copy number in patients with schizophrenia. This increase was apparent in the neurons from the prefrontal cortex of patients and in iPSC-derived neurons with a 22q11 deletion (Bundo et al. 2014). Through whole-genome sequencing, the authors determined that the L1 insertions were concentrated in gene areas related to schizophrenia and synaptic function. Recently, Doyle and colleagues analyzed 36 postmortem brains of individuals diagnosed with schizophrenia, specifically looking at dorsolateral prefrontal cortex neurons. The researchers reported a drastic increase

in intragenic novel L1s in the schizophrenia brains when compared to age-matched controls, and many L1 insertions were found within genes related to "cell projection" and "postsynaptic membrane" (Doyle et al. 2017). With a different approach, Misiak and colleagues instead investigated L1 methylation in peripheral blood leukocytes from 48 patients with first-episode schizophrenia. Upon analysis, the authors observed significantly lower L1 methylation in patients with schizophrenia who had a history of childhood trauma compared to schizophrenia patients without childhood trauma or healthy controls (Misiak et al. 2015). Existing research has shown low L1 methylation is also seen in other mental disorders, including major depressive disorder and post-traumatic stress disorder.

L1 and Major Depressive Disorder—Major Depressive Disorder (MDD) is a common disorder consisting of episodes of depressed mood that most typically affects individuals ages 25–44 (Kessler et al. 2003; Kupfer et al. 2012) (Figure 2). Both genetic and environmental factors have been associated with MDD (Mill and Petronis 2007; Tsankova et al. 2007), and L1 and other mobile elements are considered environmental stress sensors in the brain (Erwin et al. 2014; Muotri et al. 2009). In 2016, Liu and colleagues obtained peripheral blood of 105 MDD patients, and using qPCR, an increase in L1 copy number was seen in MDD patients when compared to controls (Liu et al. 2016). Additionally, authors reported lower methylation levels of L1 5' UTR in MDD patients (Liu et al. 2016), suggesting the increase in L1 activity resulted from hypomethylation.

L1 and Post-Traumatic Stress Disorder—Post-traumatic stress disorder (PTSD) is an anxiety disorder that has no particular age of onset (Figure 2), but typically follows a psychologically traumatic event (Shalev 2009). Although the molecular mechanism is still to be determined, epigenetic factors are being investigated in this field of research. In 2013, Rusiecki and colleagues obtained blood samples from 75 US military service members with a post-deployment diagnosis of PTSD and DNA methylation patterns were analyzed. The researchers reported that L1 was hypomethylated in the PTSD cases when compared to controls (Rusiecki et al. 2012; Macia et al. 2017a). The above studies have provided evidence of L1 activity mental illness in the young adult brain, however in the following section, we will explore the element's presence in a mature, adult brain affected by different neurodegenerative diseases.

3- The adult brain

L1 and Frontotemporal Lobar Degeneration—Frontotemporal lobar degeneration (FTLD) is a form of dementia characterized by a progressive decline in behavior and language (Baralle et al. 2013; Cruts et al. 2013; Rohrer et al. 2015), with an onset age of 65 (Onyike 2013) (Figure 2). This disorder is associated with the accumulation of TAR DNA-binding protein 43 (TDP-43) containing cytoplasmic inclusions (Cohen et al. 2011). In 2012, a study demonstrated binding between TDP-43 and L1-derived RNA transcripts (Li et al. 2012). Specifically, in FTLD patients with a mutated TDP-43, this binding is reduced, which results in an elevation of L1 transcripts (Li et al. 2012). Amyotrophic lateral sclerosis (ALS) is a neuromuscular disease that is also associated with mutations in *TDP-43*. Recent research has suggested activation of HERV-K, another transposable element, in sporadic ALS patients

(Li et al. 2015). These studies demonstrate how L1 and other transposable elements could possibly contribute to TDP-43 related and other neurodegenerative diseases.

L1 and Alzheimer's disease—Alzheimer's disease (AD) is a neurodegenerative disorder consisting of progressive impairments in memory and cognitive abilities (Blennow et al. 2006), with the majority of diagnosed individuals age 65 and older (Figure 2). Existing research has suggested epigenetic changes, particularly DNA methylation, as a contributor to late onset AD. In 2011, Bollati and colleagues used bisulfite-PCR pyrosequencing to evaluate methylation of L1 in about 40 AD patients and healthy controls. The authors reported an increase of L1 in AD patients when compared to controls (Bollati et al. 2011). Additionally, a mini mental state examination was performed on AD patients and those with high levels of L1 methylation performed the best (Bollati et al. 2011). On the other hand, in 2014, Hernandez and colleagues measured L1 DNA methylation levels in peripheral blood samples from about 30 patients with late-onset AD. Using a methylation-sensitive high-resolution melting quantitative assay, the authors detected no difference in L1 methylation between AD patients and controls (Hernandez et al. 2014). Due to the conflicting results of these two studies, further investigation is needed to understand the role of L1 methylation in AD pathogenesis. Recently, in another interesting research study relating L1 elements and memory formation, it was shown that L1 expression in adult mice hippocampus enabled long-term memory formation suggesting that genomic mosaicism originating from L1 retrotransposition is involved in cognitive processes (Bachiller et al. 2017).

L1 and Aging—Although the previous topics have discussed L1 in association with infancy, childhood, and adulthood disorders, there has been recent research exploring the role of L1 in aging. Aging is typically correlated with the accumulation of DNA damage and ineffective DNA repair mechanisms (Nijnik et al. 2007; Wilson et al. 2008; Li et al. 2008), and L1 activity has been hypothesized to be a source of DNA damage (Wallace et al. 2008). Wallace and colleagues (2008) investigated the individual roles of the endonuclease and reverse transcriptase of the L1 ORF2p with regard to cell viability, hypothesizing that mutations in each domain would decrease the deleterious effect on L1 expression. The authors generated the mutations using QuikChange Site-Directed Mutagenesis Kit, introducing expression constructs with the desired mutation to the cell lines. In HeLa and MCF7 cells, a mutated ORF2p EN domain significantly increased the number of viable cells, thought to be due to the reduction of DNA double-stranded breaks that accumulate with normal EN activity. Likewise, a mutated ORF2 RT domain also increased the amount of viable cells, however not as significant as the mutated EN. When both the EN and RT domains were mutated, the number of viable cells reached empty vector control levels. Additionally, authors performed an assay measuring expression of senescence specific ®-galactosidase to determine if L1 and ORF2 expression can induce a senescence-like state. Indeed, both L1 expression and ORF2 expression resulted in significantly higher ®-galactosidase levels than the control and is responsible for the loss of viable cells.

In 2013, Li and colleagues reported the activity of transposable elements in *Drosophila* brain during aging. By comparing TE transcripts in head tissues of flies at different ages using qPCR, the authors discovered a significant increase of expression of *R2* (a LINE-like

element) and *gypsy* (an LTR element) with age (Li et al. 2013). With the generation of a *gypsy-TRAP* reporter system, the authors had a way to measure *de novo gypsy* through GFP expression in the neurons of the mushroom body. As a result, they observed no labeled neurons in 2–4 day old animals, but saw a significant increase in GFP-labeled cells at later ages. dAGO2 is a protein necessary for TE silencing in somatic tissues (Czech and Hannon 2011). Authors used *dAGo2* mutants to disrupt the somatic TE control mechanism and detected higher expression levels of *R2* and *gypsy* in young *dAgo2* mutants, with 2–4 day old mutant animals acquiring the same transcript levels as 28-day old wild-type animals. Similarly, long-term memory performance assays were conducted displaying a reduction in memory of *dAgo2* mutants at 2–4 days old, which could be rescued with neuronal expression of *dAgo2. dAgo2* mutants also exhibited significantly shorter lifespans when compared to wildtype. In all, the authors suggest that the increase in TE activation with age contributes to neuronal decline. These results can possibly give us insight into TE activation with age in humans.

More recently, the activation of L1s in somatic tissues during aging has been explored. Sirtuin 6 (SIRT6) is a protein deacetylase and mono-ADP ribosyltransferase that interacts with KAP1 (KRAB-associated protein 1) to silence chromatin and facilitate DNA repair (Van Meter et al. 2014). Previously shown, SIRT6 KO mice exhibited premature aging syndrome (Mostoslavsky et al. 2006), while mice overexpressing SIRT6 displayed extended lifespans (Kanfi et al. 2012). In 2014, Van Meter et al. showed the importance of SIRT6 in repressing L1 activity. Using qPCR, the authors detected higher genomic L1 DNA in SIRT6 KO mouse embryonic fibroblasts when compared to WT. Furthermore, SIRT6KO cells contained hypomethylated CpG islands in the L1 5' UTR and depleted levels of H3K9me3, MeCP2, and Kap1, suggesting the vital role of SIRT6 in packaging L1 loci into transcriptionally repressive heterochromatin. SIRT6 binds to L1 loci to repress transcription, however with an accumulation in DNA damage as is the case with aging, SIRT6 will vacate those sites to perform DNA repair, consequently allowing increased L1 activity. These data can contribute to understanding SIRT6 activity in human aging.

Conclusions

The studies mentioned in this review all contribute to make the cogent case that L1 retrotransposition indeed impacts the human brain. On two different time scales, L1 can be seen throughout the evolution of the primate brain and within a human individual lifetime. At the individual level, retrotransposition during early neurodevelopment could contribute to the phenotypes associated with ASD and even late onset disorders. This novel concept might help to explain, for example, the lack of heritable genetic factors in some ASD individuals as well as specific networks responsible for the "savant" phenotype. Since the discovery of transposable elements in the 1940s, this scientific field has also made great feats. From understanding the mobilization mechanism to causing disease, our knowledge on how L1 impacts the human genome has grown. However, many questions still remain for future studies to answer. How has LINE-1 contributed to the evolution of the human brain? Can we prevent retrotransposition and therefore disease? What are the environmental factors that affect neuronal L1 retrotransposition? With the existing knowledge of L1s, future research

can now develop and design new technologies, approaches, and experiments to better understand the role of L1s in the human brain.

Acknowledgments

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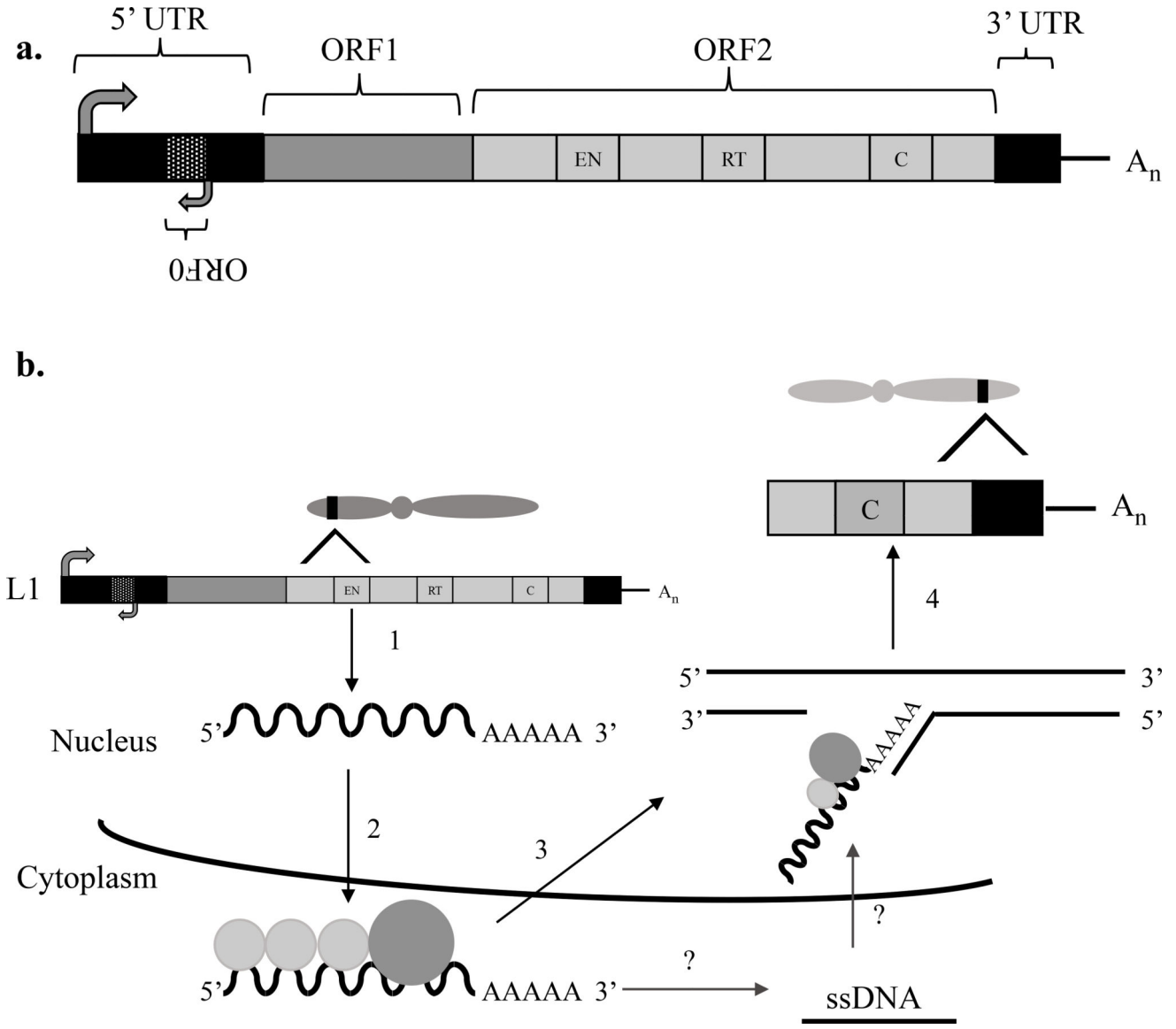
Figure 1.
a. Structure of active human L1 element. The relative positions of the 5' untranslated region (5' UTR), the open reading frames: ORF0, ORF1, and ORF2, 3' untranslated region (3' UTR), and poly A tail are shown. EN denotes endonuclease, RT denotes reverse transcriptase, and C denotes cysteine-rich domain (all encoded by ORF2). The arrows located on the 5' UTR symbolize the sense and antisense promoters. More details provided in the main text. **b.** Model of the retrotransposition cycle. 1) Generation of full-length L1 mRNA using the sense promoter in 5' UTR. 2) mRNA is transported to the cytoplasm, where ORF1p and ORF2p are translated. ORF1p and ORF2p bind to the L1 mRNA to form a ribonucleotide particle (RNP) through a process called *cis*-preference. 3) Return to the nucleus (Mechanism is still undetermined). Once in the nucleus, the ORF2 EN activity will make a break in the DNA, exposing a free 3'OH in the bottom strand, serving as a template for the RT to generate the first cDNA strand linked to the genome. 4) This mechanism called

target-primed reverse transcription (TPRT) will allow the integration of a new L1 copy. More detail provided in the main text.
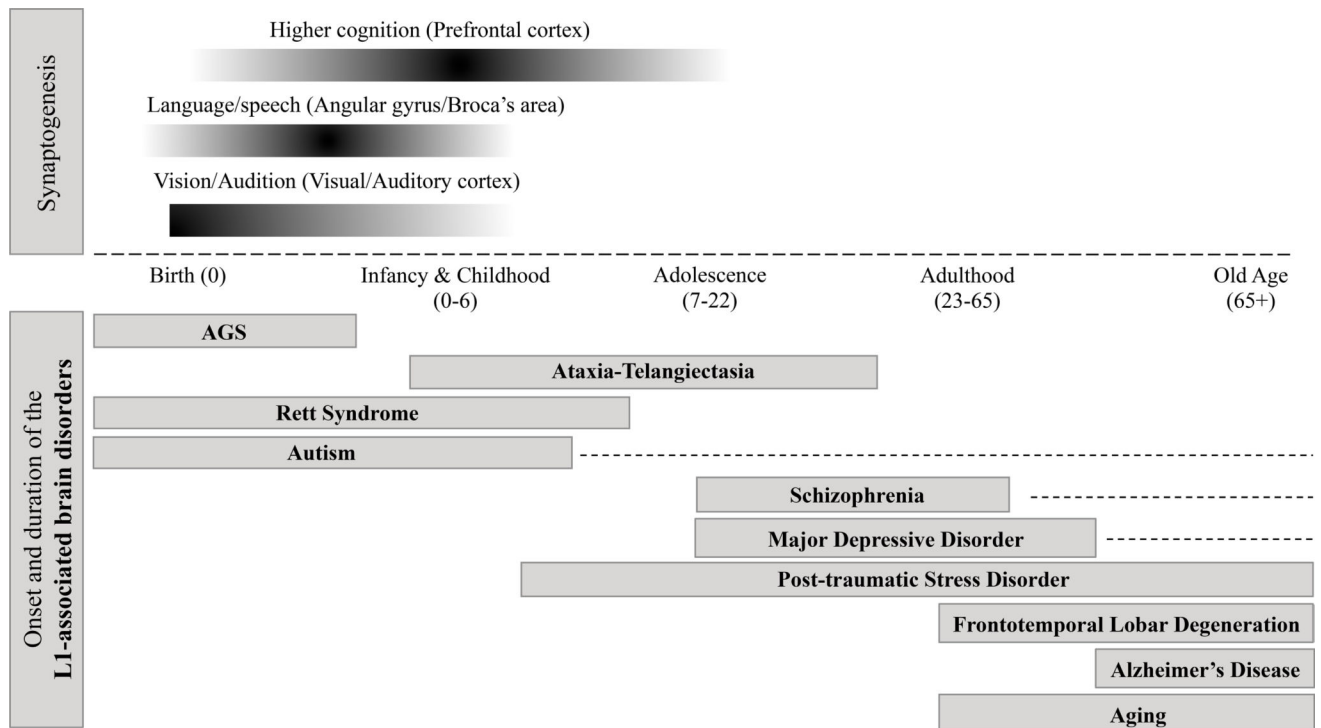
Figure 2.
Timeline of impact of L1 in the human brain during a single lifetime. The top curves represent a timeline of major events occurring in brain development from conception to adulthood (adapted from Thompson and Nelson (2001)). The L1-associated neurodevelopmental, neurodegenerative and neurological disorders discussed in the main text are graphed with respect to the age of impact in a human lifetime.