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Perspective

The *Alu* neurodegeneration hypothesis: A primate-specific mechanism for neuronal transcription noise, mitochondrial dysfunction, and manifestation of neurodegenerative disease

Peter A. Larsen[a,*], Michael W. Lutz[b], Kelsie E. Hunnicutt[a], Mirta Mihovilovic[b], Ann M. Saunders[b], Anne D. Yoder[a,c], Allen D. Roses[b,d,†]

[a]*Department of Biology, Duke University, Durham, NC, USA*
[b]*Department of Neurology, Duke University School of Medicine, Durham, NC, USA*
[c]*Duke Lemur Center, Duke University, Durham, NC, USA*
[d]*Zinfandel Pharmaceuticals, Inc, Durham, NC, USA*

Abstract It is hypothesized that retrotransposons have played a fundamental role in primate evolution and that enhanced neurologic retrotransposon activity in humans may underlie the origin of higher cognitive function. As a potential consequence of this enhanced activity, it is likely that neurons are susceptible to deleterious retrotransposon pathways that can disrupt mitochondrial function. An example is observed in the *TOMM40* gene, encoding a β-barrel protein critical for mitochondrial preprotein transport. Primate-specific *Alu* retrotransposons have repeatedly inserted into *TOMM40* introns, and at least one variant associated with late-onset Alzheimer's disease originated from an *Alu* insertion event. We provide evidence of enriched *Alu* content in mitochondrial genes and postulate that *Alus* can disrupt mitochondrial populations in neurons, thereby setting the stage for progressive neurologic dysfunction. This *Alu* neurodegeneration hypothesis is compatible with decades of research and offers a plausible mechanism for the disruption of neuronal mitochondrial homeostasis, ultimately cascading into neurodegenerative disease.

Keywords: Alternative splicing; Alzheimer's disease; Epigenetics; H3K9; Inflammation; LINE; Neuroepigenetics; Nonsense-mediated decay; Parkinson's disease; Retrotransposon; SINE; Somatic mutation; Somatic mosaicism; Spliceosome; A-to-I editing

1. Introduction

The molecular mechanisms underlying sporadic neurodegenerative disorders such as late-onset Alzheimer's disease (LOAD) and Parkinson's disease (PD) remain unclear. Although traditional genome-wide association studies (GWASs) have identified numerous candidate genes associated with both LOAD and PD, the explanatory power of these genes is low (approximately 3%–4% per locus in LOAD cases), and effective therapies that disrupt the progression of idiopathic neurodegenerative diseases have yet to be developed [1–4]. Considering this disparity, a growing number of researchers are hypothesizing a link between non-Mendelian mechanisms and sporadic neurodegenerative disease. Functional hypotheses for such mechanisms include epigenetic effects, novel structural variants influencing alternative gene splicing and gene expression, maternal inheritance of mitochondrial DNA mutations, and microbial infection [5–10]. A common thread across decades of sporadic neurodegenerative disease research is the hypothesis that mitochondrial dysfunction contributes to neuron stress and neuron degeneration, ultimately leading to the diseased state [11–19].

[†]Deceased September 30, 2016.
*Corresponding author. Tel.: 1-919-613-8727; Fax: 1-919-660-7293.
E-mail address: peter.larsen@duke.edu

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Pathologies associated with age-related neurodegenerative diseases (e.g., senile Aβ plaques, tau aggregates, cerebral atrophy, and age-related cognitive impairment) are not restricted to humans, having been identified in a number of nonhuman primates (e.g., chimpanzee, gorilla, orangutan, rhesus macaque, tamarin, and gray mouse lemur) that collectively span at least 65 million years of primate evolution [20–24]. Of these species, the one that is most distantly related to human, the gray mouse lemur (*Microcebus murinus*), routinely develops age-related pathologies (within captive individuals in established colonies) that are similar to both Alzheimer's disease (AD) and PD [25]. The evolutionary perspective that can be gleaned from the spectrum of ∼65 million years of primate evolution is critically important for understanding the origin of neurodegenerative disease in humans.

Despite the fact that primates share similar age-related disease pathologies, the manifestation of devastating human-specific symptoms associated with sporadic neurodegenerative diseases across the global distribution of our species is suggestive of a common neurologic mechanism that evolved in humans [23,24,26,27]. Following this logic, identification of the genetic factors that contribute to sporadic neurodegenerative disease in humans requires an understanding of the origin of primates and the genetic mechanisms underlying the evolution of enhanced neurologic function that separates humans from our closest primate relatives. Therefore, central to this perspective are the following observations: (1) although primates share common age-related neurodegenerative pathologies, humans display a spectrum of neurologic disorders that are uniquely human; (2) a growing body of evidence supports the hypothesis that non-Mendelian mechanisms contribute to the manifestation of neurodegenerative disease; and (3) mitochondrial dysfunction is consistently hypothesized to be associated with sporadic neurodegenerative diseases such as LOAD, PD, Huntington's disease (HD), and amyotrophic lateral sclerosis (ALS).

Here we propose a hypothesis, informed by primate evolution, for an age-related genetic mechanism that can contribute to tissue-specific mitochondrial dysfunction eventually resulting in neuronal death. It is important to note that our hypothesis centers on molecular mechanisms underlying cellular stress at the very initial stages of neurologic disease, therefore preceding macroscopic pathologies (e.g., pervasive plaque formation) that are frequently diagnostic of the disease state. We begin with the observation that structural variants of primate-specific retrotransposons (*Alu* elements) within the translocase of outer mitochondrial membrane 40 (*TOMM40*) gene are statistically associated with LOAD and that these transposable elements can influence gene function through non-Mendelian pathways. Retrotransposons are mobile elements that can replicate by reverse transcription of an RNA intermediate and then insert themselves into new locations across the genome [28]. Broadly defined, retrotransposons include long terminal repeats, long interspersed elements (LINEs), and short interspersed elements (SINEs). Of these, *Alu* elements are a highly successful primate-specific SINE and *Alus* are the most abundant mobile elements in the human genome having more than a million copies that comprise ∼11% of genomic DNA.

Although traditionally viewed as "junk DNA," a number of discoveries have shown that retrotransposons have played a fundamental role in primate evolution, including the evolution of our own species, having contributed to the formation of novel genes and gene transcription networks as well as having a role in human disease [29–35]. Moreover, retrotransposons (including *Alu*) remain active in the human central nervous system throughout life, and it is hypothesized that this activity underlies the origin of higher brain function [32,33,36,37]. We postulate that enhanced somatic retrotransposon activity in human neurologic networks is accompanied by tissue-specific mitochondrial vulnerability that increases with time and/or fluctuating epigenetic landscapes, and can thus be a contributing mechanism to sporadic neurodegeneration. This in turn leads to the specific hypothesis that retrotransposons, operating through primate or human-specific pathways, are a plausible source for environment or age-induced mitochondrial dysfunction that can ultimately contribute to neuron atrophy and death.

2. Mitochondrial integrity and neurodegenerative disease

The human brain has exceptionally high energetic demands, and metabolically active neurons depend on healthy mitochondrial populations for their survival and function. Disrupting mitochondrial homeostasis in neurons can have devastating neurologic consequences, and therefore mitochondrial dysfunction has long been hypothesized to be associated with neurologic diseases (reviewed in [38] and [39]). First proposed in 2004 by Swerdlow and Khan, the "mitochondrial cascade hypothesis" provides the framework by which mitochondrial dysfunction can contribute to the development of sporadic neurodegenerative disease [13]. Although not without controversy, the hypothesis that dysfunctional mitochondria play a role in LOAD, PD, and other neurodegenerative conditions is a consistent theme across decades of research. The mitochondrial genome encodes only 13 proteins, yet mitochondria depend on an estimated 1500 nuclear-encoded proteins for their functionality. Thus, genetic mechanisms that contribute to genomic instability of the nuclear genome, including deleterious retrotransposon-mediated pathways, can directly impact mitochondrial function and contribute to neurologic disease. A clear example involves the relationship between genetic variation of the *TOMM40* gene and neurodegenerative diseases including LOAD, PD, HD, and ALS [40].

2.1. *Insights from* TOMM40

The translocase of the outer membrane (TOM) complex is responsible for importing more than 90% of all preproteins

into the mitochondrion, and the TOM complex comprises seven subunits (Tom5, Tom6, Tom7, Tom20, Tom22, Tom40, and Tom70). Of these, Tom40 forms a β-barrel protein that is the primary channel through which mitochondrial preproteins pass, and the fully assembled TOM complex contains three Tom40 β-barrel channels arranged in a triangular pattern [41]. The *TOMM40* gene is located on human chromosome 19 and encodes 10 exons and nine introns (Fig. 1). A poorly understood yet functional and potentially important paralog of *TOMM40*, *TOMM40L*, is located on chromosome 1. Both single-nucleotide polymorphisms and short structural variants within *TOMM40* have been implicated in a number of neurologic disorders, ranging from mild cognitive impairment to major neurodegenerative diseases including LOAD and PD (reviewed in [40]) [42–44]. Amyloid precursor protein accumulates at Tom40 in AD brains, clogging the TOM complex and contributing to mitochondrial dysfunction [16]. Moreover, with respect to PD, decreasing Tom40 expression results in increasing α-synuclein accumulation and is directly correlated with an increase in reactive oxygen species, inflammation, oxidative damage, reduced adenosine triphosphate production, and an overall decrease in mitochondrial integrity [45]. Disrupting the TOM complex effectively triggers mitochondrial stress response and can ultimately lead to mitophagy, a process that has especially devastating consequences across neurologic networks [38,46,47].

Despite numerous lines of evidence that show that the TOM complex plays an essential role in mitochondrial stability, there remains an ongoing debate regarding the significance of *TOMM40* sequence variation with respect to mitochondrial dysfunction and potential consequences for neurologic disease. Much of this debate centers on the observation that *TOMM40* is in tight linkage disequilibrium with the *APOE* gene, and thus, questions have been posed as to whether there is an *APOE*-independent effect of variation within *TOMM40* and AD risk (reviewed in [40,48]). In particular, the statistical association between variable deoxythymidine homopolymer repeats within *TOMM40* intron 6 (the rs10524523 poly-T; i.e., rs523) and LOAD risk and time of onset has gained much attention. Three categorical length classes of rs523 are identified, short (S; ≤18 bp), long (L; 19–29 bp), and very long (VL; ≥30 bp) based on distributions of rs523 lengths in individuals of Caucasian ancestry [49]. The distribution of categorical length classes observed in Caucasians was also observed in individuals of African, African American, and Asian ancestry. *Cis*-haplotypes of *APOE* and rs523 are clearly delineated and are specific to ethnicity. For example, in Caucasians, the *APOE* ε4 allele is usually linked to an rs523L allele, whereas in West Africans, the *APOE* ε4 allele can be linked to either an rs523L allele or an rs523 S allele. African American *APOE*-rs523 haplotype frequencies differ from both West Africans and Caucasians and represent admixture of distinct West African and Caucasian haplotypes [50]. Several studies have reported on statistically significant associations of rs523 genotype and *APOE*-rs523 haplotypes with the risk and age of onset of AD and with cognitive decline [40,48,49,51–55]. Other meta-analyses of GWAS data have not identified a statistically significant association of rs523 with the risk or age of onset of AD independent of *APOE* genotype [56,57].

A key observation regarding the origin of rs523 that has been largely overlooked, is that rs523 is part of an *Alu* mobile element monomer that has inserted into *TOMM40* intron 6 in the antisense orientation (Fig. 1). To date, only a single study has noted the relationship between rs523 and *Alu* elements that are enriched in *TOMM40* intron 6 [58]. Indeed, Payton et al. [58] provide critical insight with respect to *TOMM40* gene expression and the presence of *Alus* within *TOMM40* introns. We expand on this observation and highlight how *Alu* retrotransposons in *TOMM40* introns 6 and 9 could contribute to transcriptional noise through enhanced nonsense-mediated

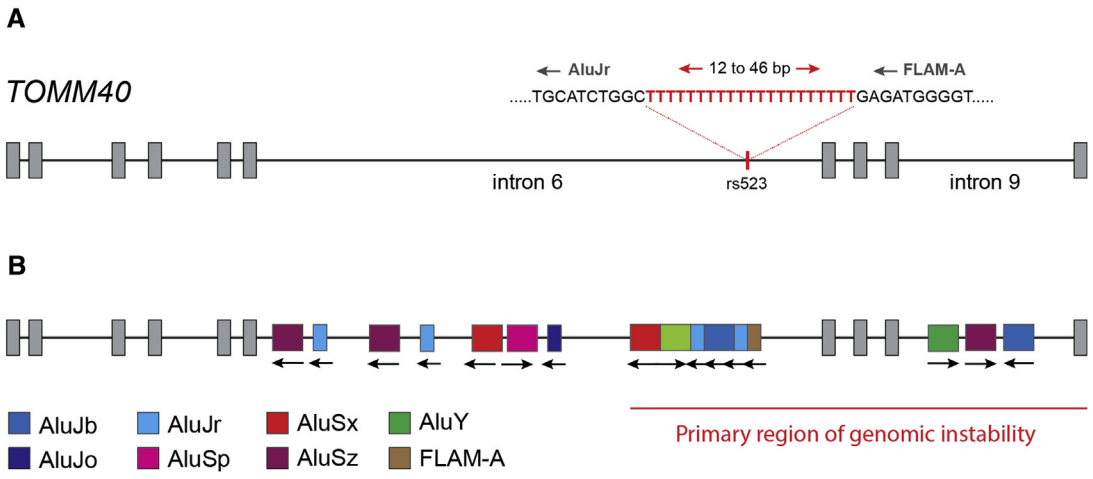

Fig. 1. Diagram of human *TOMM40* showing location of rs523 structural variant (A) and *Alu* elements (B). The primary region of genomic instability is identified as the approximate region spanning bases 44,898,490 to 44,903,725 on chromosome 19 (human genome build GRCh38/hg38). This region is hypothesized to be vulnerable to *Alu*-related mechanisms that contribute to genomic instability including alternative splicing and modification of pre-mRNA transcripts.

decay and/or the production of alternative *TOMM40* isoforms.

2.2. Alu *elements and* TOMM40 *stability*

Retrotransposons, including *Alu* elements, can have a profound influence on messenger RNA (mRNA) stability and gene transcription networks [31]. Sixteen *Alu* elements have inserted themselves across *TOMM40* introns 6 and 9, and the rs523 poly-T is part of an *Alu* element in antisense orientation. The 3′ end of *TOMM40* is particularly rich with *Alu* elements and, over evolutionary time, these have inserted themselves into the germline in both sense and antisense orientations (Fig. 1B). The relative age of each *Alu* element and the orientation of *Alu* insertion events play an essential role with respect to potential *Alu* exonization and deleterious recombination events that can disrupt *TOMM40* mRNA transcripts (Fig. 2) [29,31,58]. With respect to rs523, both poly-T and poly-A rich regions associated with intronic *Alu* elements can interrupt efficient processing of pre-mRNA transcripts by spliceosome machinery through the activation of premature polyadenylation sites and/or antagonistic binding of AU-rich binding proteins such as hnRNP C, PABP, PTB, and U2AF65 [6,31,59]. *Alu*-associated poly-T regions resulting from antisense insertion events are known to destabilize gene transcription and contribute to increasing levels of mRNA degradation [60].

Collectively, these observations identify a region of enhanced genomic instability in *TOMM40* that is vulnerable to several *Alu*-associated pathways proven to alter gene

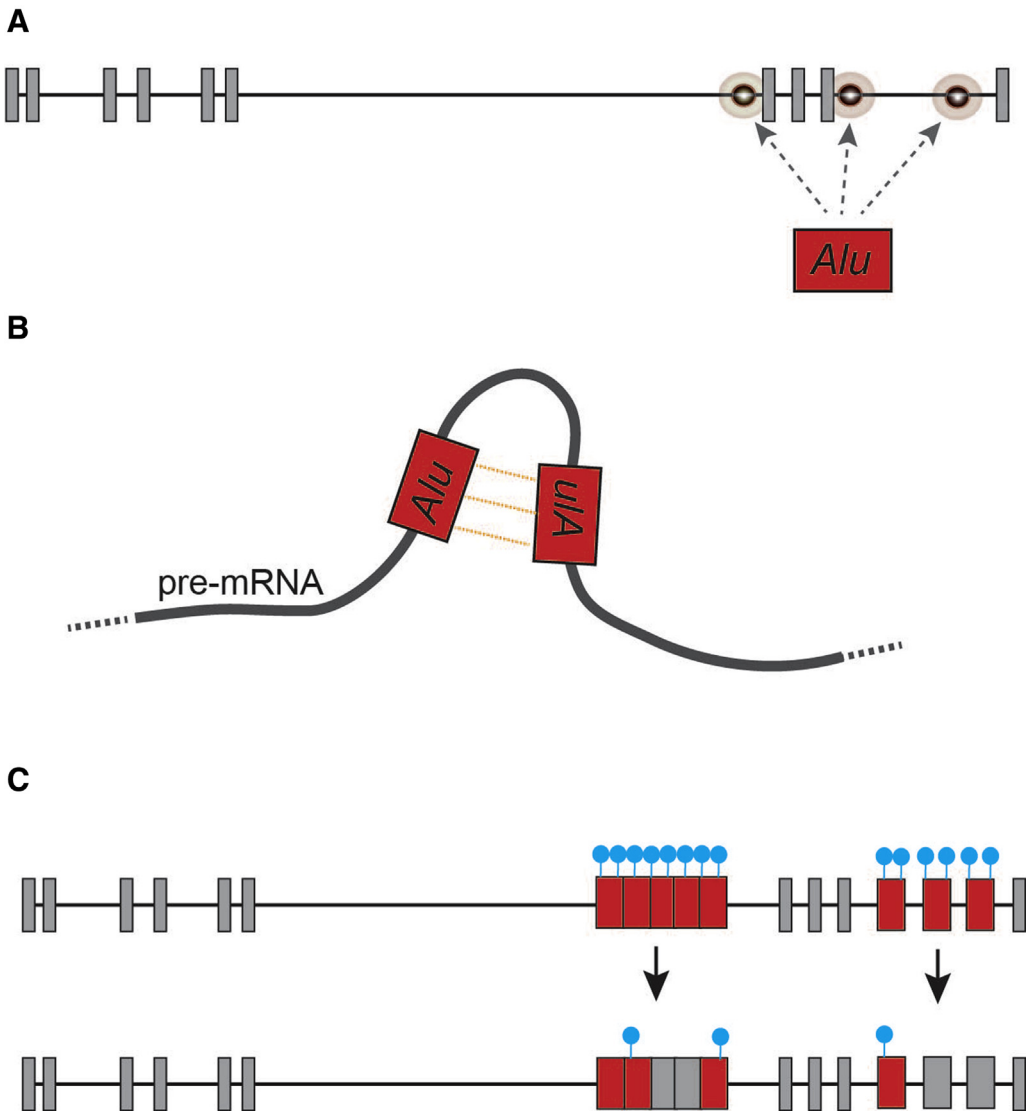

Fig. 2. Select mechanisms by which retrotransposon can influence gene splicing in somatic tissues (also see [31]). (A) de novo *Alu* retrotransposition events; (B) formation of inverted-repeat *Alu* duplexes within pre-mRNA transcripts. Such *Alu* duplexes are the primary target for tissue-specific A-to-I RNA editing pathways that can destabilize pre-mRNA transcripts [31]. (C) Hypomethylation of *Alu* contributing to exonization (blue dots represent both DNA and histone methylation landscapes).

expression and implicated in a growing list of human diseases (Fig. 2) [31]. Inverted repeat *Alus*, such as those distributed across *TOMM40* introns 6 and 9, can disrupt mRNA stability by facilitating premature transcription termination and altering adenosine-to-inosine (A-to-I) RNA editing. These pathways can also contribute to the production of altered protein conformations [31], and alternative *TOMM40* isoforms with premature termination coinciding with *Alus* (i.e., Tom40′) are identified in National Center for Biotechnology Information (NCBI) and Human Protein Atlas databases. If *Alu* elements enriched across the 3′ end of *TOMM40* are contributing to the production of modified yet functional transcripts that escape nonsense-mediated mRNA decay, then it is likely that peptides encoded by these transcripts would still be localized to the TOM complex [61]. Predictive modeling [62] of one potential alternative splicing event that coincides with *Alus* in *TOMM40* intron 9 (Tom40′; NCBI XP_005258468) suggests that a β-barrel protein conformation may still form. If so, Tom40′ would likely display functional differences from normal Tom40, perhaps serving to restrict the passage of preproteins and/or destabilize the TOM complex (Fig. 3) [61]. Moreover, an intriguing possibility with respect to the paralog *TOMM40L* is that *Alu*-associated disruption of normal mRNA processing of Tom40 could result in increased localization of Tom40L to the mitochondrial outer membrane. This conformation could alter the efficient processing of mitochondrial preproteins or otherwise destabilize the TOM complex. If accurate, such a mechanism could result in the propagation of inefficient TOM channels through mitochondrial biogenesis, fusion, and fission within individual neurons over variable time-scales (Fig. 4).

2.3. Retrotransposons, mitochondrial gene vulnerability, and neurodegenerative disease

From a broader perspective, *Alu* exonization and somatic retrotransposition events of both LINEs and *Alu* have been identified in multiple TOM genes including *TOMM5*, *TOMM7*, *TOMM22*, *TOMM40*, and *TOMM40L* [36,63,64]. These patterns indicate TOM genes are actively influenced by and are vulnerable to retrotransposons, perhaps owing to their high transcription rates and open chromatin status as hypothesized by de Andrade et al. [63]. If true, it can be predicted that nuclear-encoded mitochondrial genes would display an enrichment of mobile elements with respect to other nuclear genes. To test this prediction, we examined the mobile element content of 1145 genes that encode mitochondrial proteins [65] and an additional 8973 randomly selected protein-coding genes throughout the human genome (Supplementary Material). Our results provide statistical support for an enrichment of *Alu* mobile elements within and adjacent to mitochondrial genes (Fig. 5; Supplementary Material), consistent with previous analyses identifying enriched *Alu* content at transcriptionally active regions of the genome [66]. Thus, transcriptionally active genes essential for mitochondrial function are potentially more vulnerable

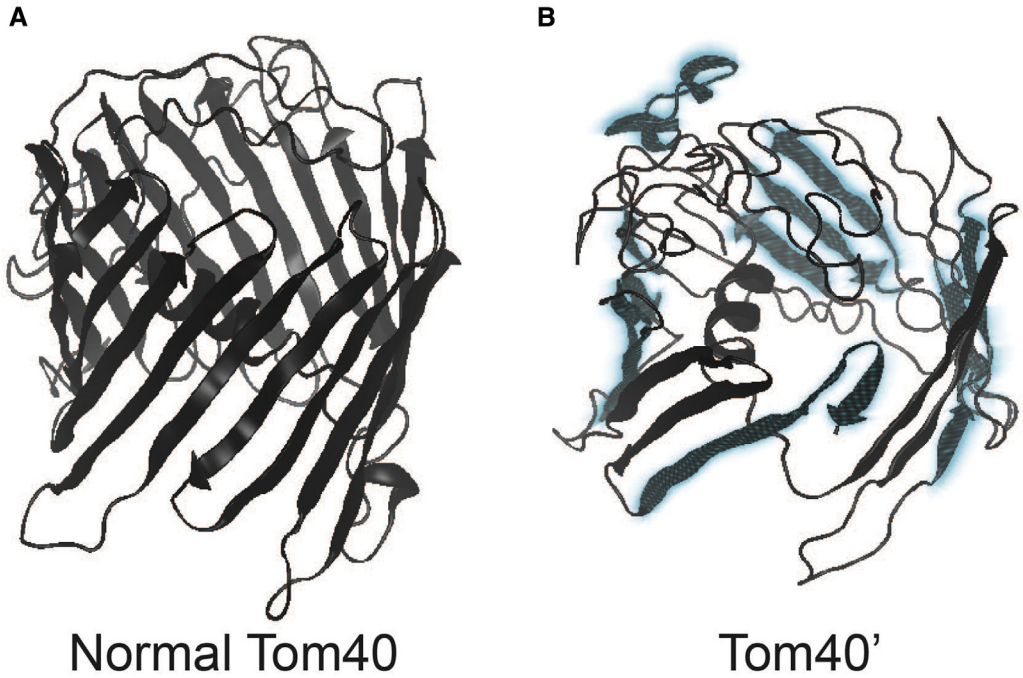

Fig. 3. Predictive model showing the potential influence of premature termination of *TOMM40* gene transcripts on Tom40 protein structure. Protein models were generated using normal (A) *TOMM40* (NCBI NP_006105; 361 amino acid sequences in length) and truncated (B) *TOMM40* (NCBI XP_005258468; 335 aa) alternative gene transcripts. The 3′ end of the truncated 335 aa transcript coincides with the *AluY* mobile element within intron 9 of *TOMM40* (a potential region of enhanced A-to-I editing; Figs. 1 and 2). Regions shaded in blue identify major conformational changes to the β-barrel protein.

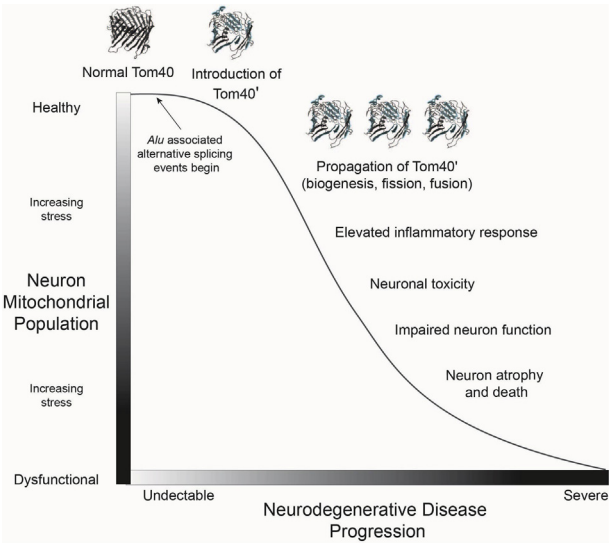

Fig. 4. Model showing the propagation of *Alu*-induced alternative conformations of Tom40, ultimately resulting in increasing levels of inflammation, neuron toxicity, and neuron death resulting in neurodegenerative disease. The model is applicable to any number of nuclear-encoded mitochondrial proteins critical to mitochondrial stability within neurons and is consistent with the broader "mitochondrial cascade hypothesis" [13]. Transcriptional noise and alternative splicing events associated with increased retrotransposon activity in neurons can contribute to mitochondrial stress over time, ultimately resulting in increasing mitochondrial stress (Y-axis) and progressive neurodegenerative disease resulting in neuron atrophy and death (X-axis).

to deleterious retrotransposon-related mechanisms known to disrupt gene expression pathways (reviewed in [31,35,67]).

If operating within energetically demanding neurons, retrotransposon-related destabilization of efficient transcription and translation of mitochondrial genes would likely contribute to the activation of inflammatory response pathways that can cascade to neuronal tissue damage and neurodegenerative disease [47]. It would therefore be anticipated that deleterious retrotransposon activity in nuclear-encoded mitochondrial genes that encode peptides occupying key functional roles would contribute to a variety of neurologic diseases. In addition to the connections observed between *TOMM40 Alu*-rs523 and LOAD [40,58], there are several striking examples that support this observation. A notable example is found with adrenoleukodystrophy, where multiple *Alu* insertion events within the *ABCD1* gene (a nuclear-encoded mitochondrial gene) contribute to deleterious nonhomologous recombination events, disrupting functional *ABCD1* peptides [68]. *ABCD1* encodes a protein of the adenosine triphosphate–binding cassette transporter family, the disruption of which contributes to functional and structural destabilization of mitochondria and is hypothesized to result in the accumulation of very long chain fatty acids throughout the nervous system [68,69]. Adrenoleukodystrophy patients suffer from progressive axonal degeneration contributing to a range of neurologic impairments, including progressive memory loss. Another example involves the *OPA1* gene where an antisense *Alu* insertion event is hypothesized to contribute to

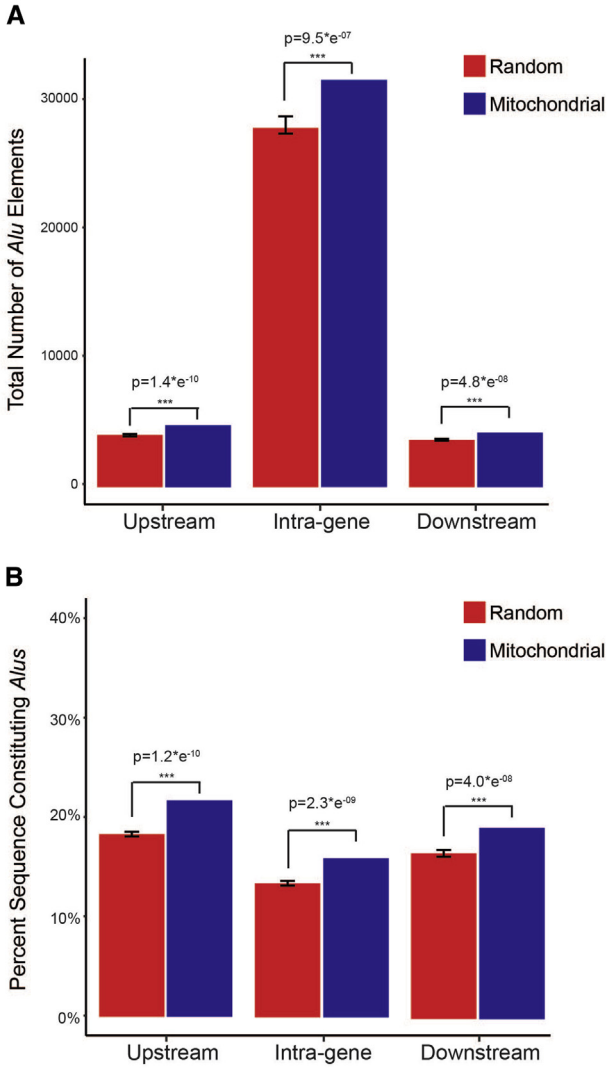

Fig. 5. *Alu* content measured across 1145 mitochondrial genes and 8973 randomly selected (non-mitochondrial) genes, as well as flanking genomic regions (5 kb), sampled from the human genome (Ensembl build GRCh38). Panel (A) shows raw number of *Alus* annotated within, and adjacent to, the sampled gene sets. Panel (B) shows the percent of bases constituting *Alu* elements within each sample. Statistical support was measured using two-tailed *t* tests and detailed methods are provided in the Supplementary Material. *** Identifies significance at $P = .05$ and error bars identify 95% confidence intervals.

alternative *OPA1* splicing events [70]. *OPA1* peptides play a key role in mitochondrial fusion and mitochondrial cristae morphology, and the *Alu*-disruption of *OPA1* expression is linked to autosomal dominant optic atrophy, a disease stemming from progressive degeneration of retinal ganglion cells ultimately resulting in optic nerve atrophy [70,71].

Alu exonization, *Alu*-mediated copy number variants, and *Alu*-mediated nonhomologous end joining have also been detected in mitochondrial genes (including mitochondria quality control genes) associated with Leigh syndrome, pyruvate dehydrogenase deficiency, presenile dementia, and PD (e.g., *NDUFS2*, *SLC30A6*, *PDHA1*, and *PARK2*) [34,64,72,73]. Collectively, these examples demonstrate

that primate-specific *Alu* mobile elements can disrupt the translation and peptide formation of nuclear-encoded mitochondrial genes, potentially contributing to the manifestation of multiple neurodegenerative disorders.

3. Mechanisms for altered gene expression and neurologic disease: an epigenetic connection

Alu elements are believed to have played a critical role in primate evolution, especially in our own species wherein increased *Alu* insertion events, human-specific SINE-Variable Number of Tandem repeat-*Alus*, human-specific *Alu*-derived exons, and enhanced neurologic *Alu* activity separate us from nonhuman primates [36,64,72,74]. Indeed, an accumulating amount of evidence indicates retrotransposons (including both LINEs and SINEs) are actively influencing human neural stem cells and somatic tissues of the brain, resulting in human-specific neurologic transcription networks [31–33,36,37,75,76]. Advanced genomic approaches, such as single-cell genome sequencing, further support this fascinating possibility and reveal that somatic retrotransposition activity in the brain contributes to the establishment of mosaic genomes of individual neurons [37,75–78]. Although potentially advantageous for higher-order cognition, this enhanced retrotransposon activity in the human central nervous system is likely accompanied by vulnerability in somatic tissue that increases with age [76].

Host genomes have evolved a number of mechanisms to defend against deleterious retrotransposon activity, including DNA and histone methylation and RNA degradation using microRNA-processing enzymes (reviewed in [31]). The epigenetic silencing of *Alu* elements is mediated by both DNA and histone H3K9 methylation to suppress transcription and retrotransposition [79,80]. Hypomethylation of *Alu* elements contributes to enhanced retrotransposon activity, which in turn can increase transcriptional noise by disrupting gene expression pathways, inducing alternative splicing events, and reducing mRNA stability [79]. Genome-wide *Alu* hypomethylation is part of the aging process and global hypomethylation of *Alu* is statistically associated with AD [81,82]. More broadly, emerging neuroepigenetic research is establishing a link between age and environment-associated epigenetic modifications and a range of neurologic disorders, from autism and schizophrenia to LOAD and PD [83]. A growing body of evidence suggests that increased retrotransposon activity in the human central nervous system, mediated by epigenetic regulation for beneficial neurologic function and the reduction of deleterious events, is accompanied by enhanced vulnerability in neurons resulting in neurologic disease [31,35,37,76].

With respect to heightened neuronal retrotransposon activity, the potential impact on neuron mitochondrial function remains unexplored. Hypomethylation of *Alu* elements and/or de novo *Alu* insertions within, or near, genes that are essential to mitochondrial function could contribute to mRNA instability, ultimately leading to mitochondrial dysfunction. Furthermore, an intriguing observation with respect to histone H3K9 methylation of *Alu* elements is that H3K9 also regulates *APOE* transcription [80]. Additional research is required to determine how the epigenetic interplay between the *Alu*-rich regions within and flanking *TOMM40* (Fig. 1; immediately upstream of *APOE* on human chromosome 19) and *APOE* can influence either *TOMM40* or *APOE* gene expression, or both. Operating within an epigenetic framework, *Alu*-related transcriptional noise of nuclear-encoded mitochondrial genes would potentially correlate with senescence and environmental exposures [84]. Tissue-specific methylation patterns of nuclear-encoded mitochondrial genes are observed in mammals and indicate specialized epigenetic modulation for the maintenance of tissue-dependent mitochondrial functional pathways, including specialized pathways in the brain [85]. Collectively, these data provide a putative epigenetic link between time-dependent mitochondrial dysfunction (both slowly accumulating or accelerated) and tissue-specific idiopathic neurodegenerative disease.

Regarding the coevolution of mitochondrial organelles and eukaryotes, the origin of primate-specific retrotransposons is a notably recent event. This is especially interesting when considering the enhanced neurologic retrotransposon activity that separates humans from other primates [33,36,76]. In concert with the increased longevity of modern humans, human-specific age-related neurologic diseases are perhaps indicative of increasing neurologic transcriptional noise because of a relaxation of retrotransposon control mechanisms. It is within this framework that we propose the *Alu* neurodegeneration hypothesis.

4. The *Alu* neurodegeneration hypothesis

Of all tissues in the human body, the brain has one of the highest rates of transposable element activity [32,36,75]. This phenomenon is one of the most striking characteristics that separates human neurologic gene networks from our closest primate relatives, leading Friedli and Trono (2015) to conclude that "…the endovirome [the collection of all transposable elements within the genome] and its controllers played a fundamental role in the expansion of higher brain functions that was key to the emergence of modern humans." Managing this enhanced retrotransposon activity requires exquisite control of the molecular pathways that work together to reap the evolutionary benefits of novel gene function while simultaneously preventing catastrophic events [31,32,76]. When considering the Friedli and Trono (2015) hypothesis, it is conceivable that gain-of-function associated with enhanced transposable element activity and the evolution of higher cognitive ability of modern *Homo sapiens* may be accompanied by neurologic vulnerability. In light of recent discoveries regarding the epigenetic regulation of transposable elements, such neurologic vulnerability may well correlate with age. Thus, humans, with our steadily increasing life expectancy rates, would be especially vulnerable [86].

We hypothesize that retrotransposons, operating through human-specific neurologic pathways [32,33,74,87–89],

contribute to environment and/or age-related neurodegeneration by disrupting functional mitochondrial populations within neurons. This mitochondrial disruption can occur through several retrotransposon-induced mechanisms that can influence the efficient and accurate transcription and/or translation of mitochondrial genes encoded in the nuclear genome, ultimately resulting in depauperate neuron mitochondrial populations. Considering *TOMM40*, it is plausible that *Alu*-related conformational changes (both subtle and major) of the outer and inner mitochondrial membrane pores could restrict or prevent the normal translocation of proteins, ultimately contributing to mitochondrial stress, inflammation, and mitophagy (Figs. 1–4). Importantly, the disruption of mitochondrial protein trafficking across both TOMM and translocase of inner mitochondrial membrane complexes has been implicated in several neurodegenerative diseases (AD, PD, HD, and ALS) [47]. An age-related and/or environmental-related pathway for such disruption is found in the epigenetic regulation of retrotransposons in the central nervous system. Both tissue and cell-specific hypomethylation of *Alu* elements, resulting from fluctuating epigenetic landscapes, can facilitate retrotransposon-induced mitochondrial stress.

The mechanisms by which symbiotic mitochondrial organelles coevolved with eukaryotic genomes provide a potential vulnerability with respect to recently evolved primate and or human-specific genetic mechanisms that disrupt gene stability. This vulnerability can be amplified through mitochondrial biogenesis and downstream mitochondrial fission and fusion events, thus contributing to the initial establishment of inefficient mitochondria that increase mitochondrial stress over time and limit neuron functionality, ultimately leading to a diseased state (Fig. 4) [13,15,18,19]. Under this framework, it would be expected that retrotransposon-mediated dysfunctional mitochondrial events would manifest in different neurologic tissues and in a seemingly temporally sporadic nature that is difficult to predict using traditional approaches such as GWAS. In light of emerging data regarding retrotransposon-induced mosaic genomes of individual neurons, it is likely that only advanced single-cell genomic techniques will provide the appropriate resolution for detecting retrotransposon-related mitochondrial dysfunction, as such events may be restricted to specific neuron populations arising from individual progenitor cells influenced by somatic retrotransposition during brain development [36,37,76,78].

The initiation of tissue-specific retrotransposon-induced dysfunctional mitochondrial cascade events, operating through variable intercellular and intracellular processes and occurring at different life stages, would ultimately result in diseased states that share similar underlying pathologies, such as inflammatory response activation, protein aggregation, and neurodegeneration [47,90,91], although with a spectrum of phenotypic neurologic impairments. Future studies focused on the epigenetic regulation of retrotransposons in individual neurons and across neurologic networks may elucidate the origin of a range of neurologic disorders and serve as the foundation for novel therapeutic approaches. We recommend that the "*Alu*-neurodegeneration hypothesis" be considered for sporadic tissue-specific neurodegenerative diseases wherein mitochondrial dysfunction has been identified, including AD, PD, HD, and ALS.

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Supplementary data

Supplementary data related to this article can be found at http://dx.doi.org/10.1016/j.jalz.2017.01.017.

RESEARCH IN CONTEXT

1. Systematic review: Despite enormous research effort the molecular mechanisms underlying sporadic neurodegenerative disease remain elusive. Moreover, although mitochondrial dysfunction is hypothesized to be an early indicator of multiple neurodegenerative diseases, the source of this dysfunction also remains unclear. We postulate that neurological mitochondrial populations are vulnerable to deleterious retrotransposon activity operating on nuclear-encoded mitochondrial genes.
2. Interpretation: Primate-specific *Alu* elements are enriched within nuclear-encoded mitochondrial genes, and these genes are subject to *Alu*-mediated mechanisms that contribute to transcriptional noise. It is likely that *Alu*-induced transcriptional noise of mitochondrial genes correlates with fluctuating epigenetic landscapes associated with aging and/or environmental stress.
3. Future directions: Our hypothesis can account for incipient mitochondrial dysfunction observed in sporadic neurodegenerative disease. We recommend future studies focused on the interplay between retrotransposons and nuclear-encoded mitochondrial gene expression and protein formation. Such research may provide new therapeutic approaches that could alleviate the earliest stages of mitochondrial and cellular stress within neurological networks, thereby preventing neurodegenerative cascades.

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