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Alu elements, evolution of the human brain, and the spectrum of neurological disease

Peter A. Larsen[*1,2], Kelsie E. Hunnicutt[1], Roxanne J. Larsen[3], Anne D. Yoder[1,2], and Ann M. Saunders[4]

[1]Department of Biology, Duke University, Durham, NC 27712

[2]Duke Lemur Center, Duke University, Durham, NC 27712

[3]Duke University School of Medicine, Duke University, Durham, NC 27710

[4]Zinfandel Pharmaceuticals, Inc., Research Triangle Park, NC 27709

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***Corresponding Author:**

Peter A. Larsen

130 Science Drive, Box 90338

Department of Biology

Duke University

Durham, NC 27708

peter.larsen@duke.edu

Abstract

Alu elements are a highly successful family of primate-specific retrotransposons that have fundamentally shaped primate evolution, including the evolution of our own species. *Alu*s play critical roles in the formation of neurological networks and the epigenetic regulation of biochemical processes throughout the central nervous system (CNS), and thus are hypothesized to have contributed to the origin of human cognition. Despite the positive aspects of *Alus*, deleterious *Alu* activity is associated with a number of neurological and neurodegenerative disorders. In particular, neurological networks are potentially vulnerable to the epigenetic dysregulation of *Alu* elements operating across the suite of nuclear-encoded mitochondrial genes that are critical for both mitochondrial and CNS function. Here, we highlight the beneficial neurological aspects of *Alu* elements as well as their potential to cause disease by disrupting key cellular processes across the CNS. We identify at least 37 neurological and neurodegenerative disorders wherein deleterious *Alu* activity has been implicated as a contributing factor for the manifestation of disease and, for many of these disorders, this activity is operating on genes that are essential for proper mitochondrial function. We conclude that the epigenetic dysregulation of *Alu* elements can ultimately disrupt mitochondrial homeostasis within the CNS. This mechanism is a plausible source for the incipient neuronal stress that is consistently observed across a spectrum of sporadic neurological and neurodegenerative disorders.

Keywords: A-to-I editing, Alzheimer's disease, brain connectome, epigenetics, mitochondria, mosaic brain

List of Abbreviations:

A-to-I: adenosine-to-inosine

AD: Alzheimer's Disease

ADAR: adenosine deaminase acting on RNA

ALS: Amyotrophic Lateral Sclerosis

AMPA: α-amino-3-hydroxy-5methyl-4-isoxazole propionate

APP: amyloid precursor protein

CNS: central nervous system

FLAM: free left *Alu* monomer

LINE: long interspersed element

L1: long interspersed element-1

LTR: long-terminal repeat

mRNA: messenger RNA

PD: Parkinson's Disease

pre-mRNA: precursor messenger RNA

SINE: short-interspersed element

TOMM: translocase of outer mitochondrial membrane

Introduction

Retrotransposons are mobile genetic elements that utilize an RNA intermediate to copy and paste themselves throughout the genome. There are two primary groups of retrotransposons, those having long-terminal repeats (LTRs) and those without (non-LTR) (Cordaux and Batzer 2009). In the human genome, non-LTR retrotransposons consist of long interspersed elements (LINEs) and short interspersed elements (SINEs) and these collectively account for a remarkable ~33% of total genome sequence (Cordaux and Batzer 2009). *Alu*

76 elements are primate-specific SINEs that are approximately 300 nucleotides in length and are
77 abundant in the human genome, with over 1.3 million elements accounting for at least 11% of
78 overall DNA sequence (Deininger et al. 2003; Hancks and Kazazian 2016). Although once
79 considered to be useless 'junk DNA', the prevalence and diversity of *Alu* elements across
80 primate genomes is suggestive of a functional advantage. A growing body of evidence
81 documents that *Alu* elements have fundamentally shaped primate evolution by facilitating
82 genome innovation through novel gene formation, elevated transcriptional diversity, long
83 non-coding RNA and microRNA evolution, transcriptional regulation, and creation of novel
84 response elements (Vansant and Reynolds 1995; Norris et al. 1995; Britten 1997; Lev-Maor
85 et al. 2003; Polak and Domany 2006; Laperriere et al. 2007; Lin et al. 2008, 2016; Lehnert et
86 al. 2009; Cordaux and Batzer 2009; Shen et al. 2011; Töhönen et al. 2015; Luco 2016; Chen
87 and Yang 2017). In light of the functional benefits that *Alus* provide primates, it is interesting
88 to note that *Alu* retrotransposition events occurred at an estimated 15-fold higher rate in the
89 human, chimpanzee, and bonobo lineage (as compared to other great apes) and a 2.2-fold
90 higher rate in humans when compared to chimpanzee and bonobo (Hedges et al. 2004; Prüfer
91 et al. 2012; Hormozdiari et al. 2013). These evolutionary patterns indicate positive selection
92 is acting to maintain *Alu* elements in primate genomes, especially within humans (Mattick
93 and Mehler 2008; Tsirigos and Rigoutsos 2009).
94 One of the most fascinating and biologically important aspects of *Alu* elements is that
95 they serve an important role in the formation and function of the brain connectome (Oliver
96 and Greene 2011; Li and Church 2013; Smalheiser 2014; Sakurai et al. 2014; Prendergast et
97 al. 2014; Linker et al. 2017). Several lines of evidence connect *Alu* elements with
98 neurogenesis and neuronal biochemical processes, including somatic retrotransposition in
99 developing neurons (in parallel to L1 retrotransposition; Baillie et al. 2011; Kurnosov et al.
100 2015) and elevated adenosine-to-inosine (A-to-I) RNA editing in the brain (Mehler and

101 Mattick 2007; Kurnosov et al. 2015; Behm and Öhman 2016). In particular, epigenetic A-to-I
102 editing plays a significant role in mediating neuronal gene expression pathways (Tariq and
103 Jantsch 2012) with *Alus* serving as the primary target for RNA editing in primates (Picardi et
104 al. 2015; Behm and Öhman 2016). Beyond RNA editing mechanisms, human neuronal gene
105 pathways are regulated by noncoding RNAs originating from *Alu* elements (e.g., BC200 and
106 NDM29) and particular *Alu* subfamilies contain retinoic acid response elements which help
107 to regulate neural patterning, differentiation, and axon outgrowth (Vansant and Reynolds
108 1995; Laperriere et al. 2007; Maden 2007; Castelnuovo et al. 2010; Smalheiser 2014). There
109 is a deep connection between *Alus* and the formation and function of primate neurological
110 networks, and this has led to the hypothesis that *Alu* elements were essential for development
111 of the transcriptional diversity and regulation required for the genesis of human cognitive
112 function (Mattick and Mehler 2008; Oliver and Greene 2011; Li and Church 2013; Sakurai et
113 al. 2014).
114 Despite the functional benefits that *Alus* have provided primate genomes, *Alu*
115 elements can disrupt gene expression and function through many pathways (Figure 1)
116 (Deininger and Batzer 1999; Deininger 2011; Tarallo et al. 2012; Ade et al. 2013; Elbarbary
117 et al. 2016; Varizhuk et al. 2016). For this reason, the genome tightly regulates *Alus* using
118 both DNA methylation and histone (H3K9) modification in order to control their expression
119 and *de novo* retrotransposition (Varshney et al. 2015; Elbarbary et al. 2016; Mita and Boeke
120 2016) and there is mounting evidence indicating that the loss of these epigenetic control
121 mechanisms (due to aging, cellular senescence, environmental factors and stress) contributes
122 to many forms of cancer, diabetes, osteoporosis, and several neurologic and
123 neurodegenerative disorders (Szpakowski et al. 2009; Belancio et al. 2010; Muotri et al.
124 2010; Jintaridth et al. 2013; Dannlowski et al. 2014; Erwin et al. 2014; Bundo et al. 2014;
125 Sun et al. 2014; Goodier 2016; Neven et al. 2016; Bedrosian et al. 2016; Shpyleva et al.

126 2017; Thongsroy et al. 2017). With respect to deleterious *Alu* pathways and neurological
127 disease, there are at least 37 neurological and neurodegenerative disorders wherein *Alu*
128 elements are hypothesized to disrupt key cellular processes, thereby resulting in or
129 contributing to the diseased state (Table 1).

130 Given the tight connection between *Alu* elements and the formation and function of
131 the nervous system, it is likely that the dysregulation of *Alu* elements contributes to many
132 sporadic or idiopathic neurological disorders observed across the global human population
133 (Larsen et al. 2017). Here, we highlight both the beneficial neurological aspects of *Alu*
134 elements as well as their potential to cause neurological disease. We focus on a novel
135 hypothesis that identifies a potential epigenetic vulnerability to neurological networks that
136 has likely escaped purifying selection. The *Alu* neurodegeneration hypothesis (sensu Larsen
137 et al. 2017) posits that the epigenetic dysregulation of *Alu* elements ultimately serves to
138 disrupt mitochondrial homeostasis in neurological networks, thereby setting the stage for
139 increased neuronal stress and neurodegeneration. Given this hypothesis, it is noteworthy that
140 many of the *Alu*-disrupted genes associated with neurological disorders are related to
141 mitochondrial function and trafficking, including nuclear-encoded mitochondrial genes (i.e.,
142 mitonuclear) which help to regulate oxidative stress and metabolic processes in the CNS
143 (Table 1). Mitochondrial dysfunction is implicated across the spectrum of neurological and
144 neurodegenerative disorders that are observed in humans and this pattern is suggestive of a
145 genetic vulnerability that has evolved in humans. Considering this, we begin by reviewing the
146 integral role that *Alu* elements have played in human evolution through brain-specific
147 epigenetic A-to-I RNA editing pathways and neurological network formation. Although these
148 *Alu*-related processes are hypothesized to have contributed to the origin of human cognition,
149 they are likely accompanied by age or stress-related vulnerabilities to the CNS, with
150 mitochondrial pathways being especially sensitive.

151 ***Alu* elements, A-to-I editing, and evolution of the human brain**

152 *Alu* elements are non-randomly distributed throughout the genome. They occur most
153 frequently within introns and are enriched within genes involved in metabolic, cellular
154 transport, and binding pathways (Grover et al. 2003; de Andrade et al. 2011). *Alu* nucleotide
155 sequences and lengths (~300 bp) are generally conserved (Batzer and Deininger 2002) and it
156 is this seemingly simple aspect of *Alu* biology that is of monumental biological importance.
157 When inserted within a gene at opposite orientations and at close proximity, *Alus* bind upon
158 themselves post-transcriptionally, resulting in the formation of a duplex stem-loop structure
159 that is stabilized by the *Alu* nucleotide sequence and length (Figure 2; Athanasiadis et al.
160 2004). These *Alu*-based secondary structures fundamentally alter the shape of pre-mRNA
161 molecules and serve as the primary binding site for ADAR proteins, which bind to the
162 double-stranded pre-mRNA duplex and edit adenosine (A) residues to inosine (I) thereby
163 recoding pre-mRNAs (Figure 2). When operating in coding regions (either directly or
164 indirectly), the translation machinery interprets the resulting I residues as guanosine (G) and
165 this mechanism accounts, in part, for the incredible diversity observed in the human proteome
166 that is not encoded within the original DNA sequence (Nishikura 2016). However, the vast
167 majority of A-to-I editing operating on *Alu* elements occurs within pre-mRNA introns and 3'
168 UTRs and this can directly influence gene regulation and function in a surprising number of
169 ways, including: the creation of novel splice donor and acceptor sites that result in *Alu*
170 exonization and alternative gene splicing (Nishikura 2016); recoding of exons immediately
171 adjacent to *Alus* (Daniel et al. 2014); disruption of RNAi pathways (Chen and Carmichael
172 2008); production of novel micro-RNA regulatory sites (Borchert et al. 2009); and increased
173 nuclear retention of promiscuously edited mRNAs (Chen and Carmichael 2008).

174 Although A-to-I editing plays an essential role in generating transcriptional diversity
175 across eukaryotes, *Alu* elements provide primate-specific RNA editing opportunities. An

176 example of this is found when comparing the rodent-specific SINE B1 family to *Alu*. Both
177 B1 and *Alu* SINE families originated from 7SL RNA (Ullu and Tschudi 1984; Vassetzky et
178 al. 2003) yet rodent-specific B1 elements are approximately half the length (~140 bp) of
179 primate *Alus* (~300 bp) and have greater levels of intra-nucleotide variation. When
180 considering the functional mechanics of A-to-I editing (Figure 2), the shorter lengths and
181 more variable rodent B1 elements result in the formation of shorter and less-stable double-
182 stranded stem-loop structures in rodent pre-mRNAs. Thus, the molecular properties that
183 separate rodent B1 from primate *Alu* translate to key functional genomic differences that have
184 influenced evolutionary processes within each lineage (Eisenberg et al. 2005; Neeman et al.
185 2006; Picardi et al. 2015; Tan et al. 2017).

186 A-to-I editing associated with *Alu* elements is perhaps one of the most functionally
187 important yet underappreciated aspect of *Alu* biology. Approximately 90% of A-to-I editing
188 within primate gene networks centers on *Alu* elements and this has fundamentally shaped
189 primate evolution, including the evolution of our own species where A-to-I editing is
190 estimated to occur at over 100 million sites in the human transcriptome (Bazak et al. 2014).
191 Moreover, recent data supports a connection between A-to-I editing and neurological
192 network formation, with elevated editing levels occurring throughout neurogenesis (Behm
193 and Öhman 2016). Genes encoding for key neurological proteins involved in
194 neurotransmission, neurogenesis, gliogenesis, and synaptogenesis are subject to enhanced A-
195 to-I editing and thus a number of studies have hypothesized a strong link between A-to-I
196 RNA editing pathways and brain development and function (Schmauss and Howe 2002;
197 Mehler and Mattick 2007; Tan et al. 2009; Sakurai et al. 2014; Liscovitch et al. 2014; Behm
198 and Öhman 2016; Hwang et al. 2016; Picardi et al. 2017b). A recent analysis of A-to-I
199 editing in over 8,500 human samples identified tissue specific editing patterns with elevated
200 editing levels in the brain, including unique patterns in the cerebellum (Tan et al. 2017). The

201 vast majority of these neurologic A-to-I editing events are operating on *Alu* elements and,
202 when combined with human-specific *Alu* evolution (Hedges et al. 2004; Cordaux and Batzer
203 2009; Prüfer et al. 2012; Hormozdiari et al. 2013), this observation serves as the foundation
204 for the hypothesis that *Alu* elements and *Alu*-related pathways contributed to the evolution of
205 enhanced human cognitive abilities (Mattick and Mehler 2008; Li and Church 2013).
206 Given the relationship between *Alu*-centric A-to-I editing and the formation and
207 function of the CNS, it is important to expand upon the neuro-specific functions of ADAR
208 proteins. Three ADAR proteins are identified (ADAR1, ADAR2, and ADAR3) and these
209 proteins have distinct tissue-specific expression patterns (Picardi et al. 2015; Tan et al. 2017).
210 ADAR1 and ADAR2 co-opt to regulate neuronal activity by editing key neurotransmitter
211 receptors and ion channels in the CNS (Hood and Emeson 2011). Interestingly, both ADAR2
212 and ADAR3 have unique brain-specific expression patterns with ADAR2 being highly
213 expressed in the brain and ADAR3 exclusively expressed in the brain (Mehler and Mattick
214 2007). Until recently the functional role of the brain-specific ADAR3 protein was largely
215 unknown, however, Oakes et al. (2017) discovered that ADAR3 competes with ADAR2 to
216 regulate glutamate receptor subunit B (*GRIA2*) A-to-I editing. The *GRIA2* protein forms a
217 critical subunit of α-amino-3-hydroxy-5methyl-4-isoxazole propionate (AMPA) receptors,
218 which regulate synaptic calcium and are involved with synaptic plasticity, memory, and
219 learning (Wright and Vissel 2012). Remarkably, A-to-I editing of a specific adenosine
220 nucleotide within *GRIA2* results in an amino acid change that alters the GluR-2 protein
221 conformation, thus disrupting calcium permeability of the AMPA receptor and potentially
222 contributing to epilepsy, amyotrophic lateral sclerosis (ALS), and schizophrenia (see Oakes
223 et al. 2017). In light of Oakes et al. (2017), the brain-specific expression pattern of ADAR3
224 indicates that this protein helps to offset A-to-I editing by ADAR2, perhaps serving to
225 mediate enhanced RNA editing processes throughout the CNS.

226 Considering the essential role that A-to-I editing processes play in the CNS, the
227 dysregulation of these processes can have a profound impact on the stability of neurological
228 networks (Mehler and Mattick 2007; Rice et al. 2012; Hwang et al. 2016). With respect to
229 ADAR proteins, mutations within ADAR1 have been linked to Aicardi-Goutières syndrome
230 (characterized by severe brain dysfunction; Rice et al. 2012) and *Alu*-related alternative
231 splicing events of ADAR2 are linked to glioma (Li et al. 2015). Disruption of ADAR1
232 editing increases production of unedited RNAs which interact with MAV proteins in the
233 outer mitochondrial membrane, ultimately serving to activate inflammatory response
234 pathways (Bajad et al. 2017; Gallo et al. 2017) and perhaps providing a mechanism for
235 inflammatory diseases of the CNS (Hofer and Campbell 2016). ADAR2 knockout mice
236 display epileptic seizures and neuronal death caused by an influx of calcium owing to the
237 disruption of *GRIA2* editing (see above). The interference of A-to-I editing processes
238 associated with the *KCNA1* gene (encoding a protein essential for potassium regulation and
239 neuron excitability) is hypothesized to underlie Episodic Ataxia Type-1 disorder, a disease of
240 the CNS characterized by seizures, stress-induced ataxia, and myokymia (Ferrick-Kiddie et
241 al. 2017). Moreover, a reduction of A-to-I editing has been observed within hippocampal
242 tissues of Alzheimer's brains versus healthy controls (Khermesh et al. 2016). From a broader
243 perspective, the disruption of A-to-I editing processes across the CNS has been linked to a
244 wide variety of neurologic and neurodegenerative disorders including major depression and
245 suicide, epilepsy, schizophrenia, Alzheimer's disease (AD), and ALS (Gurevich et al. 2002;
246 Kawahara et al. 2004; Kwak and Kawahara 2005; Maas et al. 2006; Kubota-Sakashita et al.
247 2014; Khermesh et al. 2016; Weissmann et al. 2016; Gal-Mark et al. 2017).
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250

251 ***Alu* elements, neurogenesis, and the human brain connectome**

252 There is a strong connection between *Alu* A-to-I editing and the development and
253 function of the brain, therefore it is impossible to disentangle *Alus* from the formation and
254 function of neurologic networks (Mehler and Mattick 2007; Tan et al. 2009; Behm and
255 Öhman 2016). It is estimated that the human brain is comprised of over 100 billion neurons
256 that are organized into functional hubs or parcels collectively forming the brain connectome
257 (Van Den Heuvel and Sporns 2013). Beyond major structures of the brain (e.g., cerebellum,
258 frontal cortex, hippocampus, etc.), the existence of connectome parcels shared across
259 unrelated individuals is indicative of an evolutionary conserved process underlying
260 neurological network formation and operating throughout neurogenesis. For example, a
261 recent study mapped the cerebral cortex using multi-modal magnetic resonance imaging and
262 identified 180 connectome parcels that were largely shared across 210 healthy adults (Glasser
263 et al. 2016). Understanding the molecular processes that contribute to the formation of the
264 human brain connectome is essential for understanding the origin of human-specific
265 neurological disorders and diseases observed across the global distribution of our species.
266 This is especially true for neurodegenerative conditions that are hypothesized to originate in
267 functional network hubs and progress along neuronal network connections (e.g., AD; Seeley
268 2017).

269 A growing body of evidence indicates that retrotransposons (including both LINEs
270 and SINEs) are active throughout neurogenesis and contribute to mosaic neuron genomes that
271 ultimately form the human brain connectome (Muotri et al. 2005; Erwin et al. 2014;
272 Kurnosov et al. 2015; Evrony 2016; Paquola et al. 2016; Linker et al. 2017). Although
273 somatic L1 retrotransposition events within developing neurons have received much
274 attention, it is noteworthy that *Alu* retrotransposition occurs in parallel with L1 throughout
275 neurogenesis (Baillie et al. 2011; Kurnosov et al. 2015), thus providing primate-specific

276 aspects of neurologic network formation. Furthermore, there is evidence that unites *Alu*
277 elements with retinoic acid regulation (Vansant and Reynolds 1995; Laperriere et al. 2007),
278 which is essential for neuronal patterning and differentiation throughout neurogenesis and is
279 a potential regulator of neuron regeneration (Maden 2007). Retinoic acid is vital for the
280 establishment, maintenance, and repair of neuronal networks and, given the presence of
281 retinoic acid response elements in *Alu* elements, it is possible that *Alu* activity during
282 neurogenesis is connected to retinoic acid signaling processes.

283 Considering the *Alu* regulatory pathways discussed above, it is of great interest to
284 note that retrotransposition of *Alu* elements is hypothesized to occur at elevated levels within
285 the dentate gyrus of the hippocampus, the putative site of adult neurogenesis (Kurnosov et al.
286 2015). Moreover, A-to-I editing levels steadily increase as neural progenitor cells develop
287 into adult neurons (Behm and Öhman 2016). Thus, two retrotransposon-centric processes
288 (somatic retrotransposition of both LINES and SINES and enhanced A-to-I editing operating
289 primarily on *Alu* elements) have been identified as major contributors to neurogenesis,
290 perhaps serving to establish the neuronal and biochemical diversity that underlies the ~100
291 billion neuron brain connectome. Identifying vulnerabilities to these retrotransposon-centric
292 processes will likely contribute to the identification of novel mechanisms that can result in
293 neurologic disease as well as novel therapeutic interventions.

294

295 **Pathways to incipient neuronal stress and neurological disease**

296 The disruption of *Alu*-centric epigenetic RNA editing processes is implicated across
297 the entire spectrum of neurologic disorders (see above). In light of this observation, it is
298 interesting to note that another, seemingly unrelated, feature of many neurological disorders
299 is mitochondrial dysfunction (Lin and Beal 2006; Rugarli and Langer 2012; Gottschalk et al.
300 2014; Petschner et al. 2017). However, we have previously shown that mitonuclear genes are

301 enriched with *Alu* elements when compared to random (Larsen et al. 2017), which is
302 consistent with earlier observations regarding the non-random insertion of *Alu* elements into
303 genes associated with transcriptionally active regions of the genome (Grover et al. 2003; de
304 Andrade et al. 2011). Thus, it is likely that *Alu*-mediated gene regulatory processes are
305 actively influencing mitonuclear gene expression, regulation, and protein function through
306 the pathways discussed above and reviewed in (Chen and Yang 2017). Knowing this, the
307 dysregulation of epigenetic *Alu* regulatory pathways is a plausible source for mitochondrial
308 stress and dysfunction, with the CNS being particularly vulnerable (Larsen et al. 2017). Such
309 a mechanism could contribute to the initial activation of complex mitochondrial stress
310 pathways and incipient neuronal stress associated with sporadic neurologic disorders (e.g.,
311 inflammation, immune response, mitophagy, etc.). Importantly, these processes would
312 precede macroscopic pathologies such as protein aggregation and neuronal atrophy observed
313 in neurodegenerative diseases (Swerdlow et al. 2010; Larsen et al. 2017; Swerdlow 2017).
314 The *Alu* neurodegeneration hypothesis (*sensu* Larsen et al. 2017) proposes a 'double-
315 edged sword', whereby the beneficial *Alu*-related processes that underlie neuron diversity and
316 function also have the potential to disrupt mitochondrial homeostasis across neurological
317 networks through deleterious cascade events that are facilitated by eroding tissue-specific *Alu*
318 epigenetic control mechanisms. The stability of the brain's connectome and the entire CNS
319 depends on healthy mitochondrial populations within neurons, astrocytes, microglia and
320 supporting cells (Cai et al. 2011; Viader et al. 2011; Schwarz 2013; Jackson and Robinson
321 2017). Mitochondria play critical roles for a wide range of essential neuronal processes
322 including glucose and lipid metabolism, metal ion biosynthesis, cellular trafficking along
323 axons, neurotransmitter relay across synapses, and synaptic calcium homoeostasis (Schwarz
324 2013; Harbauer et al. 2014). Therefore, molecular mechanisms that are known to disrupt gene

325 expression and protein folding of genes that are essential for mitochondrial function can
326 ultimately disrupt neurological function.

327 Interference of mitochondrial dynamics across the CNS is consistently hypothesized
328 to occur during the earliest stages of neurological and neurodegenerative disorders ranging
329 from depression, epilepsy, and schizophrenia to ALS, AD, and Parkinson's disease (PD) (Lu
330 2009; Rezin et al. 2009; Kim et al. 2010; Coskun et al. 2012; Martin 2012; Gottschalk et al.
331 2014; Larsen et al. 2017; Flippo and Strack 2017; Petschner et al. 2017). Collectively,
332 neurological disorders are estimated to impact approximately 250 million people globally,
333 accounting for at least 10.2% of the global disease burden (GBD 2015 Neurologic Disorders
334 Collaborator Group 2017). The occurrence of sporadic forms of human-specific neurologic
335 disorders (e.g. non-familial schizophrenia, ALS, late-onset AD, PD, etc.) across the entire
336 distribution of our species is suggestive of a common yet complex genetic mechanism that
337 evolved in primates and is amplified in humans (Larsen et al. 2017). Considering this, we
338 expand on the mitocentric view of idiopathic neurologic disease manifestation by reviewing
339 the evidence that unites primate-specific *Alu* activity with incipient neurologic mitochondrial
340 dysfunction.

341 Eukaryotic mitochondria are hypothesized to have originated from an endosymbiotic
342 alphaproteobacterium which, over expansive evolutionary time, evolved in parallel with host
343 genomes into the mitochondrial organelles that we observe today (Roger et al. 2017). The
344 human mitochondrial genome encodes only 13 proteins yet it is estimated that human
345 mitochondria depend on approximately ~2,000 genes encoded within the nuclear genome for
346 their functionality (Calvo et al. 2015; Johnson et al. 2017). These mitonuclear genes are thus
347 subject to deleterious *Alu* activity and *Alu*-related deleterious events have been linked to
348 many neurologic and neurodegenerative disorders, including epilepsy, Wilson's disease,
349 Leigh syndrome, PD, ALS, and AD (Table 1 and references therein; Figure 3). When

350 considering the incipient mitochondrial dysfunction observed across the spectrum of
351 neurological neurodegenerative disorders, it is possible that tissue-specific epigenetic
352 dysregulation of *Alu* elements within the CNS can ultimately manifest into distinct disease
353 phenotypes (Larsen et al. 2017).

354 Several interesting patterns emerge when examining the key neurologic processes that
355 are disrupted through deleterious *Alu* activity (Table 1). For example, mitochondria play an
356 essential role in maintaining intra-cellular metal ion homeostasis (e.g., iron, copper, and
357 zinc), the disruption of which can result in the increased production of free radicals that
358 damage mitochondria and contribute to the increased production of reduced oxygen species
359 (ROS; Rossi et al. 2004; Madsen and Gitlin 2007). The brain is especially sensitive to ROS
360 production, and iron, copper, and zinc-related oxidative stress has been linked to many
361 neurodegenerative disorders including AD, PD, and Wilson's disease (Rossi et al. 2004;
362 Madsen and Gitlin 2007). It is notable that deleterious *Alu* activity has been identified in
363 several genes that are essential to maintaining proper iron and copper homeostasis, including
364 *FXN*, *ATP7A*, *ATP7B*, *HMBS*, *NDUFS2*, *SLC30A6*, and *PARK7* (*DJ-1*) (Table 1; Gu et al.
365 2007; Kaler 2011; Girotto et al. 2014). Knowing this, it is possible that either global or tissue-
366 specific dysregulation of *Alu* elements within mitonuclear genes can alter mitochondrial
367 metal ion processing pathways thereby contributing to increased ROS production leading to
368 neurologic stress.

369 A second interesting pattern with respect to deleterious neurologic *Alu* activity
370 concerns metabolic pathways. The efficient processing of glucose and lipids across the CNS
371 is critical for the stability and function of neurons, and the disruption of mitochondrial-
372 mediated metabolic pathways has been linked to many neurologic disorders including AD
373 and peripheral neuropathies (Viader et al. 2013; De La Monte and Tong 2014). Deleterious
374 *Alu* activity occurs in genes that are critical for glucose and lipid metabolism, including

375 *ABCD1*, *ACAT1*, *ALMS1*, *APOB*, *GK*, *GLA*, *HPRT*, *LPL*, *PDHA1, PMM2*, *PSEN1, SOD2* and
376 *SPAST* (Table 1). Several of these genes encode for mitochondrial-related proteins that have
377 been implicated in metabolic diseases that directly, or indirectly, contribute to neurological
378 dysfunction. The connection between *Alu* elements and metabolic pathways is consistent with
379 the observation that *Alu* elements preferentially insert into metabolic genes, and this has led
380 to the hypothesis that *Alus* regulate the expression of genes related to Type 1 Diabetes
381 (Grover et al. 2003; Mirza et al. 2014; Kaur and Pociot 2015). Moreover, *Alu* RNAs act to
382 suppress the expression of both endothelial nitric oxide synthase (eNOS) and superoxide
383 dismutase 2 (SOD2) during hyperglycemic conditions (Wang et al. 2016), suggesting a
384 regulatory role of *Alu* elements during oxidative stress and strengthening the link between
385 *Alu* element activity and diabetes.

386 There is growing evidence linking sporadic AD with dysfunctional metabolic
387 pathways, leading some to consider AD as a 'Type 3 Diabetes' wherein glycolysis and lipid
388 homeostasis is altered (Steen et al. 2005; De La Monte et al. 2006; De La Monte and Wands
389 2008; De La Monte and Tong 2014; De Felice and Lourenco 2015; Mittal et al. 2016). The
390 most well-documented risk factor for AD is a variant within *APOE* (*APOE* ε4), a gene which
391 encodes for a glycoprotein that that mediates cholesterol and lipid transport (Saunders et al.
392 1993; Strittmatter et al. 1993; Mahley and Rall 2000). The *APOE* ε4 allele is strongly
393 associated with earlier onset of AD, and it is hypothesized that this is a result of the
394 disruption of cholesterol processing and subsequent accumulation of amyloid precursor
395 proteins (APP; i.e., the Amyloid cascade hypothesis). Although the 'Amyloid cascade
396 hypothesis' has dominated Alzheimer's research for decades (Hardy and Higgins 1992;
397 Selkoe 2000; McKhann et al. 2011), the failure of multiple drug trials targeting amyloid
398 pathways has led many in the Alzheimer's research community to search for alternative

399 hypotheses that can help explain the origin of neurodegenerative disease as well as novel
400 molecular pathways with therapeutic potential (Herrup 2015).
401 It is of particular interest then to note that a second genetic risk factor for AD,
402 *TOMM40*, is located immediately adjacent to *APOE* on human chromosome 19, and the two
403 genes are in tight linkage disequilibrium (Lyall et al. 2014; Roses et al. 2016a). *TOMM40*
404 encodes for a beta-barrel protein that ultimately forms a central pore in the outer
405 mitochondrial membrane (Shiota et al. 2015) and, much like *APOE*, genetic variants of
406 *TOMM40* are linked to cognitive impairment and neurodegenerative disease (Roses 2010;
407 Gottschalk et al. 2014; Greenbaum et al. 2014; Roses et al. 2016b; Arpawong et al. 2017).
408 The most-well known of these *TOMM40* variants is the rs10524523 (rs523) homopolymer
409 repeat, a variable stretch of deoxythymidine (T) located within *TOMM40* intron 6 (Roses
410 2010). The rs523 poly-T varies in length from approximately 12 to 46 nucleotides, and the
411 longer variants are statistically associated with thinning of the hippocampus (independent of
412 the *APOE* ε4 allele) (Burggren et al. 2017) and earlier onset of AD (Lutz et al. 2010; Roses et
413 al. 2010). Interestingly, rs523 is embedded within tandemly repeated *Alu* elements and
414 originated from an *Alu* insertion event (Larsen et al. 2017). At least 149 *Alu* A-to-I editing
415 events are identified within *TOMM40*, the majority of which are associated with *Alu* elements
416 surrounding the rs523 repeat and intron 9 (Picardi et al. 2017a).
417 There is a potentially important link that unties *APOE* APP processing with the
418 functional mechanics of pre-protein transport through the TOMM pore. It is possible that
419 conformational changes of the Tom40 protein, potentially originating from *Alu*-mediated
420 events (see above, reviewed in Elbarbary et al. 2016; Chen and Yang 2017; Larsen et al.
421 2017), can ultimately serve to restrict the passage of lipids across the outer-mitochondrial
422 membrane (Larsen et al. 2017). When combined with altered APP processing, this process
423 could account for the initial site of intra-cellular protein accumulation that is hypothesized to

424 precede extra-cellular plaque formation during very early stages of AD (Skovronsky et al.
425 1998; D'Andrea et al. 2001; Takahashi et al. 2002). Consistent with this hypothesis is the
426 direct observation of APP accumulation at the TOMM pore (Devi et al. 2006) as well as
427 functional tolerance of Tom40 conformational changes by mitochondria (Mager et al. 2011;
428 Kuszak et al. 2015). Importantly, this mechanism could help to explain the common patterns
429 of protein accumulation (e.g., amyloid plaques and alpha-synuclein Lewy bodies) observed
430 across the spectrum of neurodegenerative disease, including ALS, AD, and PD (Ross and
431 Poirier 2004; Gottschalk et al. 2014; Larsen et al. 2017). An age or stress-related component
432 to Tom40 conformational changes comes with the epigenetic dysregulation of *Alu* elements
433 associated with the aging process or traumatic stress (see Larsen et al. 2017). Whether or not
434 these processes are directly mediated by deleterious *Alu* events remains to be tested, however,
435 it is notable that *Alu* exons and *Alu* somatic retrotransposition events have been identified in
436 several TOM genes that are required for the stability of the translocase of the outer
437 mitochondrial membrane and pre-protein import, including *TOMM5*, *TOMM7*, *TOMM22*,
438 *TOMM40*, and *TOMM40L* (Baillie et al. 2011; de Andrade et al. 2011; Lin et al. 2016).
439 With respect to *Alu* elements, mitochondrial dysfunction, and the broader pathological
440 scope of AD and other neurodegenerative diseases, there is evidence suggesting that *Alu*-
441 derived peptides interact with tau proteins, perhaps serving a regulatory role for tau
442 phosphorylation (Hoenicka et al. 2002). Tau is a microtubule associated protein that
443 functions to stabilize axonal microtubules and to transport mitochondria along axons, and
444 taupathies (including tau hyperphosphorylation) are a characteristic feature of several
445 neurodegenerative diseases including AD, progressive supranuclear palsy, corticobasal
446 degeneration, and Pick's disease (Ittner and Götz 2011; Khanna et al. 2016). The *MAPT* gene
447 encodes for tau and alternative splicing events of *MAPT* result in multiple tau isoforms
448 (Reddy 2011). Approximately 86 *Alu* elements (including FLAMs) are distributed throughout

449 *MAPT* introns and A-to-I editing is occurring at 315 *Alu* related sites with elevated levels at
450 the 3' end of *MAPT* (REDIportal database; Picardi et al. 2017a). When considering the
451 potential for *Alu* structural variants of *MAPT* (including DNA and pre-mRNA secondary
452 structures) and evidence of *Alu* RNAs interacting with tau proteins (Hoenicka et al. 2002), we
453 recommend additional studies aimed at elucidating the regulatory impacts that *Alu* elements
454 might have on *MAPT* gene expression and tau phosphorylation.
455
456 **A-to-I editing and the potential for mitochondrial stress**
457 Although several neurological disorders are hypothesized to be the result of disruptive
458 A-to-I editing processes across the CNS (see above), it is presently unknown whether or not
459 these processes are actively influencing mitochondrial function. What evidence is there
460 indicating that post-transcriptional modification of mitonuclear genes can alter gene
461 expression or function? Are there particular neurological or neurodegenerative disorders that
462 are associated with mitonuclear genes that have elevated levels of A-to-I editing? To provide
463 insights into these questions, we searched the REDIportal A-to-I editing database (Picardi et
464 al. 2017a) for mitonuclear genes where 1) A-to-I editing has been identified within *Alu*
465 elements in coding regions and 2) A-to-I editing has contributed to non-synonymous amino
466 acid changes. We identified 57 mitonuclear genes with A-to-I editing occurring within
467 putative *Alu* exons and in 52 of these genes the post-transcriptional modification resulted in
468 nonsynonymous amino acid changes (Supplementary Table 1). Many of these genes are
469 involved with essential neuronal processes including calcium binding and transport, zinc
470 transport, apoptosis regulation, voltage-gated ion channels, and mitochondrial elongation
471 with notable examples including *ADSL*, *BAX*, *CASP2*, *COQ2*, *DFFB*, *FBXO18*, *LYRM4*,
472 *PACRG*, and *SLC30A6* (Supplementary Table 1).

473 From a broader perspective, we identified enhanced A-to-I editing across 134
474 mitonuclear genes that are associated with a spectrum of neurologic and neurodegenerative
475 disorders ranging from depression, tobacco use disorder, and bipolar disorder to ALS, Leigh
476 syndrome, PD, and AD (Supplementary Table 2). In light of these patterns, we hypothesize
477 that system-wide or tissue-specific epigenetic dysregulation of *Alu* A-to-I editing within the
478 CNS can serve to disrupt key mitochondrial biochemical processes, thus potentially
479 contributing to incipient mitochondrial and neuronal stress (Figure 3).
480
481 **Conclusions**
482 Enhanced somatic retrotransposon throughout neurogenesis contributes to the mosaic
483 brain, however, such activity likely contributes to mosaic pathways leading to disease (Erwin
484 et al. 2014). Elucidating these pathways might ultimately provide insight into the sporadic
485 nature of idiopathic diseases that are impacting the global human population. The disruption
486 of *Alu*-mediated pathways that underlie gene regulation is a plausible mechanism for the
487 origin of complex human-specific neurologic and neurodegenerative disorders. Although
488 many of these disorders have similar phenotypes (e.g., mitochondrial dysfunction), it is
489 possible that these phenotypes arise from deleterious activity operating across tissue-specific
490 gene networks. If correlated with eroding or fluctuating epigenetic control mechanisms of
491 retrotransposons that are associated with aging, cellular senescence, and/or cellular stress
492 (Belancio et al. 2010; Pal and Tyler 2016), then such mechanisms might largely escape
493 purifying selection and would be difficult to detect using traditional methods (e.g., genome-
494 wide association studies).
495 *Alu* elements have played a pivotal role in the evolution of the human epigenome
496 (Prendergast et al. 2014), and both hyper- and hypomethylation of *Alu* elements have been
497 correlated with a number of age-related disorders including Alzheimer's disease, multiple

498 sclerosis, osteoporosis, and many forms of cancer (Bollati et al. 2009; Jintaridth and
499 Mutirangura 2010; Belancio et al. 2010; Jintaridth et al. 2013; Neven et al. 2016). In light of
500 these patterns, as well as the newly discovered regulatory roles of *Alu* elements (Polak and
501 Domany 2006; Chen and Carmichael 2008; Chen and Yang 2017), we recommend additional
502 research that focuses on the epigenetic interplay between *Alu* elements and mitochondrial
503 gene networks in the central nervous system.
504

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508

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1081 **Figure Legends**

1082

1083 **Figure 1.** Select mechanisms whereby *Alu* elements can alter gene expression and function
1084 (also see Elbarbary et al. 2016). **A:** Sequence homology and orientation of *Alu* elements
1085 contributes to the formation of distinct secondary structures in both DNA and RNA. DNA
1086 *Alu* G-quadruplex structures can alter transcription kinetics (Varizhuk et al. 2016) and pre-
1087 mRNA *Alu* binding forms stem-loop structures that are the primary site for A-to-I editing
1088 (see Figure 2). **B:** Recombination of intra-gene *Alu* elements resulting in exon deletion. **C:**
1089 Exonification intronic *Alus* contributing to the production of alternative mRNAs. **D:**
1090 Environmental or traumatic stress cascades contribute to the increased expression of *Alu*
1091 RNAs that contribute to inflammation (Li and Schmid 2001; Tarallo et al. 2012; Hunter et al.
1092 2015; Lapp et al. 2016), the disruption of global gene transcription through Pol II binding
1093 (Mariner et al. 2008), and an increase of H3K9 histone methylation that alters *Alu* epigenetic
1094 pathways (Varshney et al. 2015; Lapp and Hunter 2016; Larsen et al. 2017).

1095

1096 **Figure 2.** Intronic *Alu* elements located in close proximity (**A**) can bind to each other within
1097 pre-mRNAs (**B**) thereby producing a stable stem-loop secondary structure that is the primary
1098 substrate for A-to-I editing in primates. ADAR proteins bind to pre-mRNA *Alu* structures
1099 (**C**) and convert adenosine residues to inosine. If occurring in coding regions, the translation
1100 machinery then interprets the inosine residues as guanosine and this can contribute to amino
1101 acid changes and alternative protein conformations (**D**).

1102

1103 **Figure 3.** Deleterious *Alu* activity operating on mitonuclear genes can disrupt mitochondrial
1104 function in the CNS and contribute to a number of diseased phenotypes (see Table 1). The
1105 type and severity of associated neurological and neurodegenerative disorders depends on the

1106 deleterious *Alu* mechanism of action, the mitonuclear gene pathways involved, the time or
1107 developmental stage of induction, and tissue specificity (see Larsen et al. 2017). If operating
1108 across the suite of mitonuclear genes through epigenetic pathways, the mechanism helps to
1109 explain the origin of incipient mitochondrial stress and CNS connectome destabilization that
1110 is observed across the spectrum of neurological and neurodegenerative disorders.
1111
1112
1113

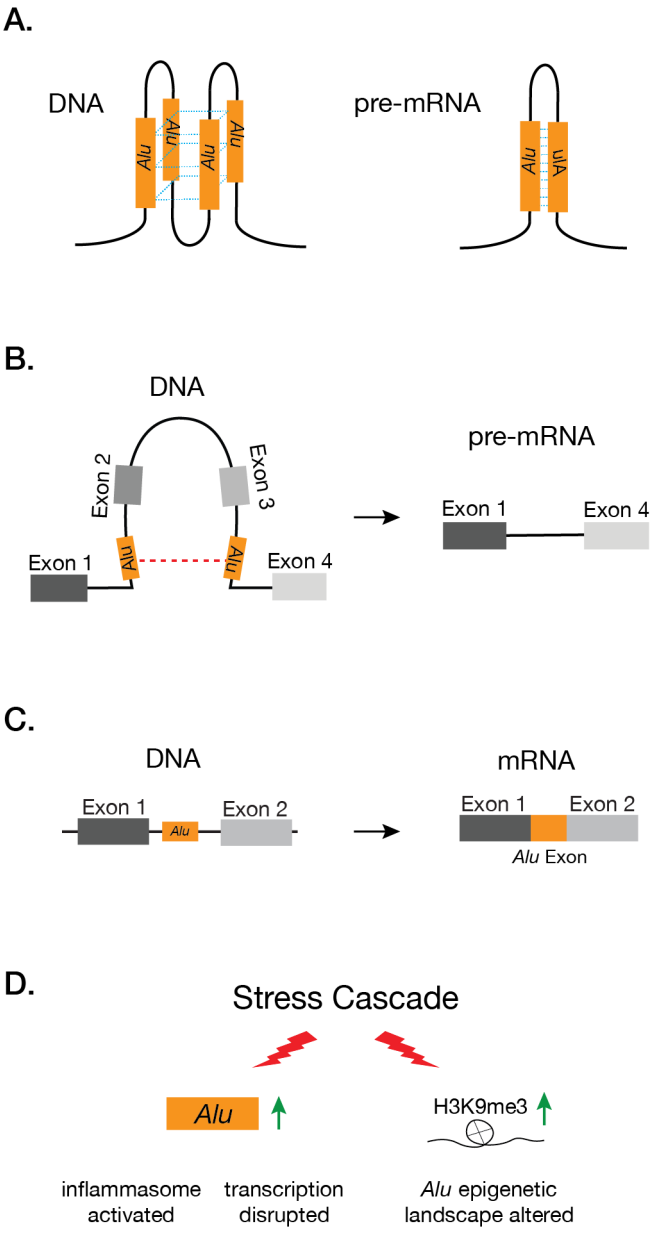
A.
DNA
Alu
Alu
Alu
Alu
pre-mRNA
Alu
Alu
B.
DNA
Exon 2
Exon 3
Exon 1
Alu
Alu
Exon 4
pre-mRNA
Exon 1
Exon 4
C.
DNA
Exon 1
Alu
Exon 2
mRNA
Exon 1
Exon 2
Alu Exon
D.
Stress Cascade
Alu
H3K9me3
inflammasome activated
transcription disrupted
Alu epigenetic landscape altered

Figure 1.

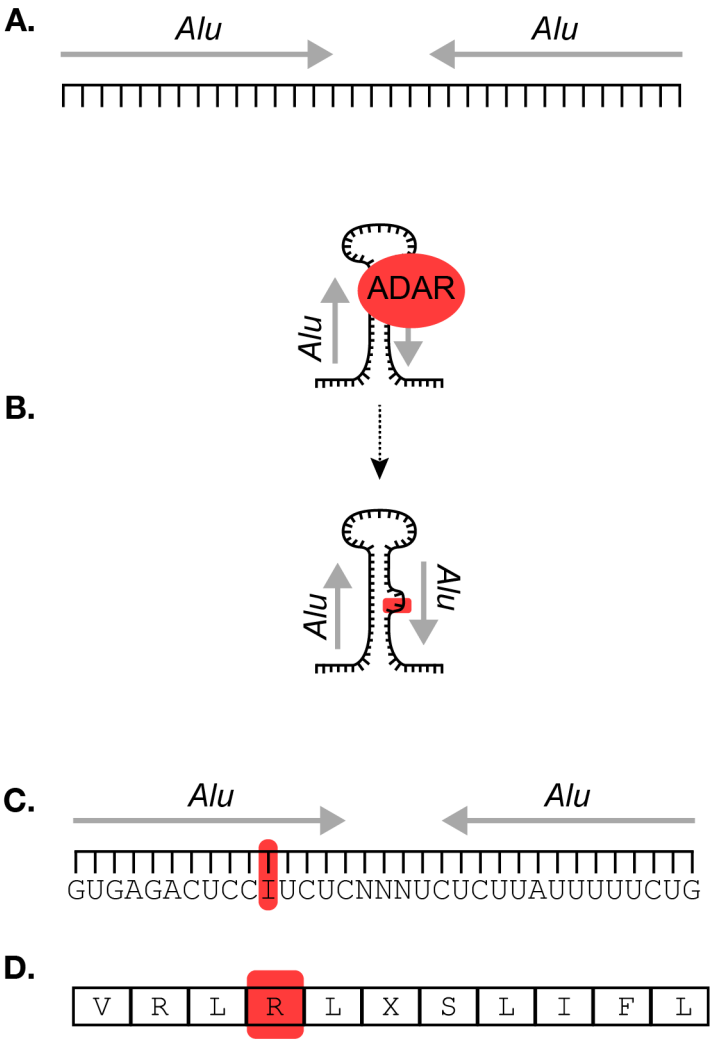
A.
Alu
Alu
B.
ADAR
Alu
Alu
Alu
C.
Alu
Alu
GUGAGACUCCIUCUCNNNUCUCUUAUUUUUCUG
D.
V R L R L X S L I F L

Figure 2.

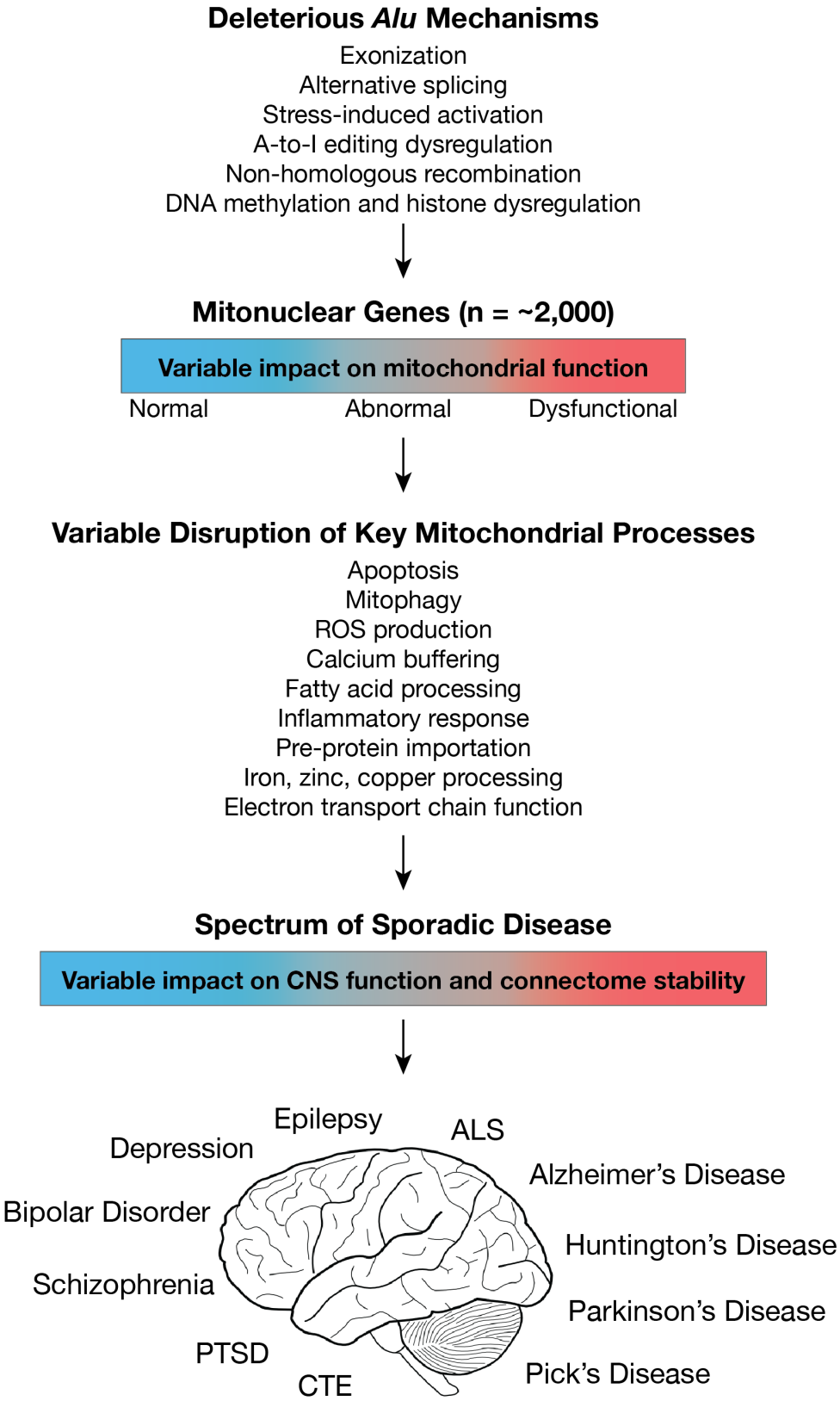
Deleterious *Alu* Mechanisms
Exonization
Alternative splicing
Stress-induced activation
A-to-I editing dysregulation
Non-homologous recombination
DNA methylation and histone dysregulation
Mitonuclear Genes (n = ~2,000)
Variable impact on mitochondrial function
Normal
Abnormal
Dysfunctional
Variable Disruption of Key Mitochondrial Processes
Apoptosis
Mitophagy
ROS production
Calcium buffering
Fatty acid processing
Inflammatory response
Pre-protein importation
Iron, zinc, copper processing
Electron transport chain function
Spectrum of Sporadic Disease
Variable impact on CNS function and connectome stability
Epilepsy
ALS
Depression
Alzheimer's Disease
Bipolar Disorder
Huntington's Disease
Schizophrenia
Parkinson's Disease
PTSD
Pick's Disease
CTE

Figure 3.

Table 1. Genes associated with neurological and neurodegenerative disorders wherein deleterious *Alu* activity has been documented experimentally or is hypothesized to disrupt gene function. Gene names in bold identify genes essential for mitochondrial function and transport and/or are associated with mitochondrial abnormalities (sensu Dawson et al. 1995, Calvo et al. 2015, Zempel and Mandelkow 2015, Bhattachargee et al. 2016, Chong-Chong et al. 2016, Checler et al. 2017, Johnson et al. 2017, Wang et al. 2013). For additional *Alu* associated diseases see Hancks and Kazazian (2016) and Payer et al. (2017). Asterisks identify genes where mutations result in dysregulation of *Alu* elements.

Gene Name	Disorder	*Alu* Mechanism of Disruption	Reference
ABCD1	Adrenoleukodystrophy	Deletion events	Kutsche et al. 2002
ACAT1 (T2)	Mitochondrial acetoacetyl-CoA thiolase deficiency	Deletion event	Zhang et al. 2006
ACE	Alzheimer's disease	Insertion events	Wu et al. 2013
ADAR2	Glioma	Exonization	Li et al. 2015
ALDH7A1	Pyridoxine-dependent epilepsy	Recombination	Mefford et al. 2015
ALMS1	Alström syndrome	Insertion event	Taşkesen et al. 2012
APOB	Hypobetalipoproteinemia	Recombination	Huang et al. 1989
ATP5J	Alzheimer’s disease	Duplication	Antonell et al. 2012
ATP7A	Menkes disease	Insertion event	Gu et al. 2007; Bhattacharjee et al. 2016
ATP7B	Wilson's disease	Alternative splicing	Mameli et al. 2015
C9orf72	ALS, FTLD	Loss of epigenetic control, elevated *Alu* transcripts	Prudencio et al. 2017
CHD7	CHARGE syndrome	Deletion	Udaka et al. 2007
CLN3	Batten disease	Deletion	Lerner et al. 1995
COL4A5	Alport syndrome	Deletion and exonization	Nozu et al. 2014
DICER1*	Age-related macular degeneration	*Alu* RNA build-up with reduced DICER1 activity	Kaneko et al. 2011; Kim et al. 2014
FXN	Friedreich's Ataxia	*Alu* repeat expansion, alternative splicing events	Pandolfo 2006
GK	Glycerol kinase deficiency	Insertion event	Zhang et al. 2000
GLA	Fabry disease	Deletion event	Dobrovolny et al. 2011
HPRT	Lesch-Nyhan disease	Recombination	Brooks et al. 2001
HMBS	Acute intermittent prophyria	Insertion event	Mustajoki et al. 1999
LPL	Lipoprotein lipase deficiency	Complex deletion-insertion	Okubo et al. 2007
MFN2 (CMT2a)	Charcot-Marie-Tooth type 2A	Copy number variants	Pehlivan et al. 2016
MPO	Alzheimer’s disease	*Alu* hormone response variant; estrogen dysregulation	Reynolds et al. 1999

NDUFS2	Leigh Syndrome	Exonization	Larsen et al. 2017
NF1	Neurofibromatosis type I	Deletion and chimeric gene fusion	Wimmer et al. 2011; Ferrari et al. 2017
NFIX	Marshall-Smith syndrome	Deletions	Schanze et al. 2014
OPA1	Autosomal Dominant Optic Atrophy	Alternative splicing events	Gallus et al. 2010
PARK2	Parkinson's disease	Recombination	Morais et al. 2016
PARK7 (DJ-1)	Parkinson's disease	Deletion	Bonifati et al. 2002
PDHA1	Pyruvate Dehydrogenase Deficiency	Exonization	Larsen et al. 2017
PIGL	CHIME syndrome	Deletion	Knight Johnson et al. 2017
PMM2	Congenital disorders of glycosylation type Ia	Complex deletion	Schollen et al. 2007
POMT1	Walker Warburg syndrome	Insertion	Bouchet et al. 2007
PSEN1	Alzheimer’s disease	Deletion	Le Guennec et al. 2017
PXMP2 (PMP22)	Charcot-Marie-Tooth type 2A	*Alu*-*Alu*-mediated rearrangement	Choi et al. 2011; Gu et al. 2015
RP2 (NUDT19)	X-linked retinitis pigmentosa	*Alu*-L1 recombination	Schwahn et al. 1998, Jiang et al. 2017
SLC6A4	Depression, reduced hippocampal volume	Altered promoter methylation	Dannlowski et al. 2014
SLC25AC	Intellectual disability	Deletion	Vandewalle et al. 2013
SLC30A6	Alzheimer's disease, Dementia, ALS	Gene fusion event	Boone et al. 2014
SMN1	Spinal muscular atrophy	Exonization, deletion events, circularization	Ottesen et al. 2017
SOD2	Hyperglycemia	Repressed expression	Wang et al. 2016
SOX10	Waardenburg syndrome type 4	Deletion	Bondurand et al. 2012
SPAST	Autosomal-dominant spastic paraplegia 4	Deletions, CNVs, gene fusion events	Boone et al. 2014
SPG7	Hereditary spastic paraplegia	Deletion, recombination	Arnoldi et al. 2008; López et al. 2015
SPG11	Hereditary spastic paraplegia	Deletion	Conceição et al. 2012
STAU1	Myotonic Dystrophy Type 1	Alternative splicing regulation	Bondy-Chorney et al. 2016
TDP-43	ALS, frontotemporal lobar degeneration	Transposable element dysregulation	Li et al. 2012
TOMM40	Late-Onset Alzheimer's Disease	*Alu* repeat expansion, putative alternative splicing events	Larsen et al. 2017
TRIM37	Mulibrey nanism	Deletion events	Jobic et al. 2017