11 Jan 2018

Warning SINEs: *Alu* elements, evolution of the human brain, and the spectrum of neurological disease

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Running title: *Alu* elements and the spectrum of neurological disease

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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 benefits that *Alus* provide, 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

51 **List of Abbreviations:**

52 A-to-I: adenosine-to-inosine

53 AD: Alzheimer's Disease

54 ADAR: adenosine deaminase acting on RNA

55 ALS: Amyotrophic Lateral Sclerosis

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

57 APP: amyloid precursor protein

58 circRNAs: circular RNAs

59 CNS: central nervous system

60 FLAM: free left *Alu* monomer

61 LINE: long interspersed element

62 L1: long interspersed element-1

63 LTR: long-terminal repeat

64 mRNA: messenger RNA

65 PD: Parkinson's Disease

66 pre-mRNA: precursor messenger RNA

67 SEDs: super-enhancer domains

68 SINE: short-interspersed element

69 TADs: topologically associating domains

70 TOMM: translocase of outer mitochondrial membrane

71

72 **Introduction**

73 Retrotransposons are mobile genetic elements that utilize an RNA intermediate to

74 copy and paste themselves throughout the genome. There are two primary groups of

75 retrotransposons, those having long-terminal repeats (LTRs) and those without (non-LTR)

76 (Cordaux and Batzer 2009). In the human genome, non-LTR retrotransposons consist of long
77 interspersed elements (LINEs) and short interspersed elements (SINEs) and these collectively
78 account for a remarkable ~33% of total genome sequence (Cordaux and Batzer 2009). *Alu*
79 elements are primate-specific SINEs that are approximately 300 nucleotides in length and are
80 abundant in the human genome, with over 1.3 million elements accounting for at least 11% of
81 overall DNA sequence (Deininger et al. 2003; Hancks and Kazazian 2016). Although once
82 considered to be useless 'junk DNA', the prevalence, diversity, and non-random distribution
83 of *Alu* elements across primate genomes is suggestive of a functional advantage. Indeed, a
84 large body of evidence documents that *Alu* elements have directly influenced primate
85 evolution by facilitating genome innovation through: novel gene formation, elevated
86 transcriptional diversity, long non-coding RNA and microRNA evolution (including circular
87 RNAs), transcriptional regulation, and creation of novel response elements (Vansant and
88 Reynolds 1995; Norris et al. 1995; Britten 1997; Lev-Maor et al. 2003; Polak and Domany
89 2006; Laperriere et al. 2007; Lin et al. 2008, 2016; Lehnert et al. 2009; Cordaux and Batzer
90 2009; Shen et al. 2011; Jeck et al. 2013; Töhönen et al. 2015; Luco 2016; Chen and Yang
91 2017). Moreover, *Alus* fundamentally alter the three-dimensional architecture and spatial
92 organization of primate genomes by defining the boundaries of chromatin interaction
93 domains (i.e., topologically associating domains (TADs); Dixon et al. 2012). A growing body
94 of evidence indicates that genome architecture has a direct influence on biological function,
95 and the observation that *Alus* are enriched within both TADs and super-enhancer domains
96 (SEDs) supports the hypothesis that *Alus* directly influence a wide range of critically
97 important processes within primates across multiple levels, from overall genome stability to
98 tissue-specific gene regulation (Huda et al. 2009; Dixon et al. 2012; Soibam 2017; Glinsky
99 2018). In light of the functional benefits that *Alus* provide primates, it is interesting to note
100 that *Alu* retrotransposition events occurred at an estimated 15-fold higher rate in the human,

101 chimpanzee, and bonobo lineage (as compared to other great apes) and a 2.2-fold higher rate
102 in humans when compared to chimpanzee and bonobo (Hedges et al. 2004; Prüfer et al. 2012;
103 Hormozdiari et al. 2013). These evolutionary patterns indicate that positive selection is acting
104 to maintain *Alu* elements in primate genomes, especially within humans (Mattick and Mehler
105 2008; Tsirigos and Rigoutsos 2009).

106 One of the most fascinating and biologically important aspects of *Alu* elements is that
107 they serve an important role in the formation and function of the brain connectome (Oliver
108 and Greene 2011; Li and Church 2013; Smalheiser 2014; Sakurai et al. 2014; Prendergast et
109 al. 2014; Linker et al. 2017; Bitar and Barry 2018). Many lines of evidence connect *Alu*
110 elements with neurogenesis and critical neuronal biochemical processes, including: somatic
111 retrotransposition in developing neurons (in parallel to L1 retrotransposition; Baillie et al.
112 2011; Kurnosov et al. 2015), formation of regulatory circRNAs that are enriched in the
113 central nervous system (CNS) and concentrated at synapses (Jeck et al. 2013; Rybak-Wolf et
114 al. 2015; Chen and Schuman 2016; Floris et al. 2017), regulation of genes that are essential
115 for proper neuron function (e.g. *ACE*, *SMN1*, *SMN2*, *SLC6A4*; Wu et al. 2013; Ottesen et al.
116 2017; Schneider et al. 2017), and elevated adenosine-to-inosine (A-to-I) RNA editing in the
117 brain (Mehler and Mattick 2007; Kurnosov et al. 2015; Behm and Öhman 2016). In
118 particular, epigenetic A-to-I editing plays a significant role in mediating neuronal gene
119 expression pathways (Tariq and Jantsch 2012) with *Alus* serving as the primary target for
120 RNA editing in primates (Picardi et al. 2015; Behm and Öhman 2016). Beyond RNA editing
121 mechanisms, human neuronal gene pathways are regulated by noncoding RNAs originating
122 from *Alu* elements (e.g., BC200 and NDM29) and specific *Alu* subfamilies contain retinoic
123 acid response elements which help to regulate neural patterning, differentiation, and axon
124 outgrowth (Vansant and Reynolds 1995; Laperriere et al. 2007; Maden 2007; Castelnuovo et
125 al. 2010; Smalheiser 2014). Moreover, recent discoveries indicate *Alu* elements underlie the

126 formation of a vast number of human-specific circRNAs that are hypothesized to play
127 important roles in neurological gene expression pathways (Jeck et al. 2013; Rybak-Wolf et al.
128 2015; Chen and Schuman 2016; Dong et al. 2017). There is a deep connection between *Alus*
129 and the formation and function of primate neurological networks, and this has led to the
130 hypothesis that *Alu* elements were essential for development of the transcriptional diversity
131 and regulation required for the genesis of human cognitive function (Mattick and Mehler
132 2008; Oliver and Greene 2011; Li and Church 2013; Sakurai et al. 2014).

133 Despite the functional benefits that *Alus* have provided primate genomes, *Alu*
134 elements can disrupt gene expression and function through many pathways (Figure 1;
135 Deininger and Batzer 1999; Deininger 2011; Tarallo et al. 2012; Ade et al. 2013; Elbarbary et
136 al. 2016; Varizhuk et al. 2016). For this reason, the genome tightly regulates *Alus* using both
137 DNA methylation and histone (H3K9 methylation) modification in order to control their
138 expression and *de novo* retrotransposition (Varshney et al. 2015; Elbarbary et al. 2016; Mita
139 and Boeke 2016) and there is mounting evidence indicating that the loss of these epigenetic
140 control mechanisms (due to aging, cellular senescence, environmental factors and stress)
141 contributes to many forms of cancer, diabetes, osteoporosis, and several mental and
142 neurodegenerative disorders (Szpakowski et al. 2009; Belancio et al. 2010; Muotri et al.
143 2010; Jintaridth et al. 2013; Dannlowski et al. 2014; Erwin et al. 2014; Bundo et al. 2014;
144 Sun et al. 2014; Goodier 2016; Neven et al. 2016; Bedrosian et al. 2016; Shpyleva et al.
145 2017; Thongsroy et al. 2017). With respect to deleterious *Alu* pathways and neurological
146 disease, there are at least 37 mental and neurodegenerative disorders wherein *Alu* elements
147 are hypothesized to disrupt key cellular processes, thereby resulting in or contributing to the
148 diseased state (Table 1).

149 Given the tight connection between *Alu* elements and the formation and function of
150 the nervous system, it is likely that the dysregulation of *Alu* elements contributes to many

151 sporadic or idiopathic neurological disorders observed across the global human population
152 (Larsen et al. 2017). Here, we highlight both the beneficial neurological aspects of *Alu*
153 elements as well as their potential to cause neurological disease. We focus on a novel
154 hypothesis that identifies a potential epigenetic vulnerability to neurological networks that
155 has likely escaped purifying selection. The *Alu* neurodegeneration hypothesis (sensu Larsen
156 et al. 2017) posits that the epigenetic dysregulation of *Alu* elements ultimately serves to
157 disrupt mitochondrial homeostasis in neurological networks, thereby setting the stage for
158 increased neuronal stress and neurodegeneration. Given this hypothesis, it is noteworthy that
159 many of the *Alu*-disrupted genes associated with neurological disorders are related to
160 mitochondrial function and trafficking, including nuclear-encoded mitochondrial genes (i.e.,
161 mitonuclear) which help to regulate oxidative stress and metabolic processes in the CNS
162 (Table 1). Mitochondrial dysfunction is implicated across the spectrum of neurological and
163 neurodegenerative disorders that are observed in humans and this pattern is suggestive of a
164 genetic vulnerability that has evolved in humans. Considering this, we begin by reviewing the
165 integral role that *Alu* elements have played in human evolution through brain-specific
166 epigenetic A-to-I RNA editing pathways and neurological network formation. Although these
167 *Alu*-related processes are hypothesized to have contributed to the origin of human cognition,
168 they are likely accompanied by age or stress-related epigenetic vulnerabilities to the CNS,
169 with mitochondrial pathways being especially sensitive.
170

171 **_Alu_ elements, A-to-I editing, and evolution of the human brain**

172 *Alu* elements are non-randomly distributed throughout the genome. They occur most
173 frequently within introns and are enriched within genes involved in metabolic, mitochondrial,
174 cellular transport, and binding pathways (Grover et al. 2003; de Andrade et al. 2011; Larsen
175 et al. 2017). *Alu* nucleotide sequences and lengths (~300 bp) are generally conserved (Batzer

176 and Deininger 2002) and it is this seemingly simple aspect of *Alu* biology that is of
177 monumental biological importance. When inserted within a gene at opposite orientations and
178 at close proximity, *Alus* bind upon themselves post-transcriptionally, resulting in the
179 formation of a duplex stem-loop structure that is stabilized by the *Alu* nucleotide sequence
180 and length (Figure 2; Athanasiadis et al. 2004). These *Alu*-based secondary structures
181 fundamentally alter the shape of pre-mRNA molecules and serve as the primary binding site
182 for ADAR proteins, which bind to the double-stranded pre-mRNA duplex and edit adenosine
183 (A) residues to inosine (I) thereby recoding pre-mRNAs (Figure 2). When operating in
184 coding regions (either directly or indirectly), the translation machinery interprets the resulting
185 I residues as guanosine (G) and this mechanism accounts, in part, for the incredible diversity
186 observed in the human proteome that is not encoded within the original DNA sequence
187 (Nishikura 2016). However, the vast majority of A-to-I editing operating on *Alu* elements
188 occurs within pre-mRNA introns and 3' UTRs and this can directly influence gene regulation
189 and function in a surprising number of ways, including: the creation of novel splice donor
190 and acceptor sites that result in *Alu* exonization and alternative gene splicing (Nishikura
191 2016); recoding of exons immediately adjacent to *Alus* (Daniel et al. 2014); disruption of
192 RNAi pathways (Chen and Carmichael 2008); production of novel micro-RNA regulatory
193 sites (Borchert et al. 2009); and increased nuclear retention of promiscuously edited mRNAs
194 (Chen and Carmichael 2008).
195 Although A-to-I editing plays an essential role in generating transcriptional diversity
196 across eukaryotes, *Alu* elements provide primate-specific RNA editing opportunities. An
197 example of this is found when comparing the rodent-specific SINE B1 family to *Alu*. Both
198 B1 and *Alu* SINE families originated from 7SL RNA (Ullu and Tschudi 1984; Vassetzky et
199 al. 2003) yet rodent-specific B1 elements are approximately half the length (~140 bp) of
200 primate *Alus* (~300 bp) and have greater levels of intra-nucleotide variation. When

201 considering the functional mechanics of A-to-I editing (Figure 2), the shorter lengths and
202 more variable rodent B1 elements result in the formation of shorter and less-stable double-
203 stranded stem-loop structures in rodent pre-mRNAs. Thus, the molecular properties that
204 separate rodent B1 from primate *Alu* translate to key functional genomic differences that have
205 influenced evolutionary processes within each lineage (Eisenberg et al. 2005; Neeman et al.
206 2006; Picardi et al. 2015; Tan et al. 2017).

207 A-to-I editing associated with *Alu* elements is perhaps one of the most functionally
208 important yet underappreciated aspect of *Alu* biology. Approximately 90% of A-to-I editing
209 within primate gene networks centers on *Alu* elements and this has fundamentally shaped
210 primate evolution, including the evolution of our own species where A-to-I editing is
211 estimated to occur at over 100 million sites in the human transcriptome (Bazak et al. 2014).
212 Moreover, recent data supports a connection between A-to-I editing and neurological
213 network formation, with elevated editing levels occurring throughout neurogenesis (Behm
214 and Öhman 2016). Genes encoding for key neurological proteins involved in
215 neurotransmission, neurogenesis, gliogenesis, and synaptogenesis are subject to enhanced A-
216 to-I editing and thus a number of studies have hypothesized a strong link between A-to-I
217 RNA editing pathways and brain development and function (Schmauss and Howe 2002;
218 Mehler and Mattick 2007; Tan et al. 2009; Sakurai et al. 2014; Liscovitch et al. 2014; Behm
219 and Öhman 2016; Hwang et al. 2016; Picardi et al. 2017b). A recent analysis of A-to-I
220 editing in over 8,500 human samples identified tissue specific editing patterns with elevated
221 editing levels in the brain, including unique patterns in the cerebellum (Tan et al. 2017). The
222 vast majority of these neurologic A-to-I editing events are operating on *Alu* elements and,
223 when combined with human-specific *Alu* evolution (Hedges et al. 2004; Cordaux and Batzer
224 2009; Prüfer et al. 2012; Hormozdiari et al. 2013), this observation serves as the foundation

225 for the hypothesis that *Alu* elements and *Alu*-related pathways contributed to the evolution of
226 enhanced human cognitive abilities (Mattick and Mehler 2008; Li and Church 2013).
227 Given the relationship between *Alu*-centric A-to-I editing and the formation and
228 function of the CNS, it is important to expand upon the neuro-specific functions of ADAR
229 proteins. Three ADAR proteins are identified (ADAR1, ADAR2, and ADAR3) and these
230 proteins have distinct tissue-specific expression patterns (Picardi et al. 2015; Tan et al. 2017).
231 ADAR1 and ADAR2 co-opt to regulate neuronal activity by editing key neurotransmitter
232 receptors and ion channels in the CNS (Hood and Emeson 2011). Interestingly, both ADAR2
233 and ADAR3 have unique brain-specific expression patterns with ADAR2 being highly
234 expressed in the brain and ADAR3 exclusively expressed in the brain (Mehler and Mattick
235 2007). Until recently the functional role of the brain-specific ADAR3 protein was largely
236 unknown, however, Oakes et al. (2017) discovered that ADAR3 competes with ADAR2 to
237 regulate glutamate receptor subunit B (*GRIA2*) A-to-I editing. The *GRIA2* protein forms a
238 critical subunit of α-amino-3-hydroxy-5methyl-4-isoxazole propionate (AMPA) receptors,
239 which regulate synaptic calcium and are involved with synaptic plasticity, memory, and
240 learning (Wright and Vissel 2012). Remarkably, A-to-I editing of a specific adenosine
241 nucleotide within *GRIA2* results in an amino acid change that alters the GluR-2 protein
242 conformation, thus disrupting calcium permeability of the AMPA receptor and potentially
243 contributing to epilepsy, amyotrophic lateral sclerosis (ALS), and schizophrenia (see Oakes
244 et al. 2017). In light of Oakes et al. (2017), the brain-specific expression pattern of ADAR3
245 indicates that this protein helps to offset A-to-I editing by ADAR2, perhaps serving to
246 mediate enhanced RNA editing processes throughout the CNS.
247 Considering the essential role that A-to-I editing processes play in the CNS, the
248 dysregulation of these processes can have a profound impact on the stability of neurological
249 networks (Mehler and Mattick 2007; Rice et al. 2012; Hwang et al. 2016). With respect to

250 ADAR proteins, mutations within ADAR1 have been linked to Aicardi-Goutières syndrome
251 (characterized by severe brain dysfunction; Rice et al. 2012) and *Alu*-related alternative
252 splicing events of ADAR2 are linked to glioma (Li et al. 2015). Disruption of ADAR1
253 editing increases production of unedited RNAs which interact with MAV proteins in the
254 outer mitochondrial membrane, ultimately serving to activate inflammatory response
255 pathways (Bajad et al. 2017; Gallo et al. 2017) and perhaps providing a mechanism for
256 inflammatory diseases of the CNS (Hofer and Campbell 2016). ADAR2 knockout mice
257 display epileptic seizures and neuronal death caused by an influx of calcium owing to the
258 disruption of *GRIA2* editing (see above). The interference of A-to-I editing processes
259 associated with the *KCNA1* gene (encoding a protein essential for potassium regulation and
260 neuron excitability) is hypothesized to underlie Episodic Ataxia Type-1 disorder, a disease of
261 the CNS characterized by seizures, stress-induced ataxia, and myokymia (Ferrick-Kiddie et
262 al. 2017). Moreover, a reduction of A-to-I editing has been observed within hippocampal
263 tissues of Alzheimer's brains versus healthy controls (Khermesh et al. 2016). From a broader
264 perspective, the disruption of A-to-I editing processes across the CNS has been linked to a
265 wide variety of mental and neurodegenerative disorders including major depression and
266 suicide, epilepsy, schizophrenia, Alzheimer's disease (AD), and ALS (Gurevich et al. 2002;
267 Kawahara et al. 2004; Kwak and Kawahara 2005; Maas et al. 2006; Kubota-Sakashita et al.
268 2014; Khermesh et al. 2016; Weissmann et al. 2016; Gal-Mark et al. 2017).
269

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

271 There is a strong connection between *Alu* A-to-I editing and the development and
272 function of the brain, therefore it is impossible to disentangle *Alus* from the formation and
273 function of neurologic networks (Mehler and Mattick 2007; Tan et al. 2009; Behm and
274 Öhman 2016). It is estimated that the human brain is comprised of over 100 billion neurons

275 that are organized into functional hubs or parcels collectively forming the brain connectome
276 (Van Den Heuvel and Sporns 2013). Beyond major structures of the brain (e.g., cerebellum,
277 frontal cortex, hippocampus, etc.), the existence of connectome parcels shared across
278 unrelated individuals is indicative of an evolutionary conserved process underlying
279 neurological network formation and operating throughout neurogenesis. For example, a
280 recent study mapped the cerebral cortex using multi-modal magnetic resonance imaging and
281 identified 180 connectome parcels that were largely shared across 210 healthy adults (Glasser
282 et al. 2016). Understanding the molecular processes that contribute to the formation of the
283 human brain connectome is essential for understanding the origin of human-specific
284 neurological disorders and diseases observed across the global distribution of our species.
285 This is especially true for neurodegenerative conditions that are hypothesized to originate in
286 functional network hubs and progress along neuronal network connections (e.g., AD; Seeley
287 2017; Cope et al. 2018).
288 A growing body of evidence indicates that retrotransposons (including both LINEs
289 and SINEs) are active throughout neurogenesis and contribute to mosaic neuron genomes that
290 ultimately form the human brain connectome (Muotri et al. 2005; Erwin et al. 2014;
291 Kurnosov et al. 2015; Evrony 2016; Paquola et al. 2016; Linker et al. 2017). Although
292 somatic L1 retrotransposition events within developing neurons have received much
293 attention, it is noteworthy that *Alu* retrotransposition occurs in parallel with L1 throughout
294 neurogenesis (Baillie et al. 2011; Kurnosov et al. 2015), thus providing primate-specific
295 aspects of neurologic network formation. Furthermore, there is evidence that unites *Alu*
296 elements with retinoic acid regulation (Vansant and Reynolds 1995; Laperriere et al. 2007),
297 which is essential for neuronal patterning and differentiation throughout neurogenesis and is
298 a potential regulator of neuron regeneration (Maden 2007). Retinoic acid is vital for the
299 establishment, maintenance, and repair of neuronal networks and, given the presence of

300 retinoic acid response elements in *Alu* elements, it is possible that *Alu* activity during
301 neurogenesis is connected to retinoic acid signaling processes.
302 Considering the *Alu* regulatory pathways discussed above, it is of great interest to
303 note that retrotransposition of *Alu* elements is hypothesized to occur at elevated levels within
304 the dentate gyrus of the hippocampus, the putative site of adult neurogenesis (Kurnosov et al.
305 2015). Moreover, A-to-I editing levels steadily increase as neural progenitor cells develop
306 into adult neurons (Behm and Öhman 2016). These data indicate that at least two
307 retrotransposon-centric processes (somatic retrotransposition of both LINES and SINES and
308 enhanced A-to-I editing operating primarily on *Alu* elements) are major contributors to
309 neurogenesis, perhaps serving to establish the neuronal and biochemical diversity that
310 underlies the ~100 billion neuron brain connectome. Remarkably, emerging data suggests
311 that a third *Alu*-centric process is associated with the formation and function of neurological
312 networks, this being the production of circRNAs that are enriched in the brain and
313 concentrated at synaptic junctions (Jeck et al. 2013; Rybak-Wolf et al. 2015; Chen and
314 Schuman 2016). Identifying vulnerabilities to each of these retrotransposon-centric processes
315 will likely contribute to the identification of novel mechanisms underlying mental disorders
316 and neurologic disease and could lead to novel therapeutic interventions.
317
318 **Pathways to incipient neuronal stress and neurological disease**
319 The disruption of *Alu*-centric epigenetic RNA editing processes is implicated across
320 the entire spectrum of neurologic disorders (see above). In light of this observation, it is
321 interesting to note that another, seemingly unrelated, feature of many neurological disorders
322 is mitochondrial dysfunction (Lin and Beal 2006; Rugarli and Langer 2012; Gottschalk et al.
323 2014; Petschner et al. 2017). However, we have previously shown that mitonuclear genes are
324 enriched with *Alu* elements when compared to random (Larsen et al. 2017), which is

325 consistent with earlier observations regarding the non-random insertion of *Alu* elements into
326 genes associated with transcriptionally active regions of the genome (Grover et al. 2003; de
327 Andrade et al. 2011). Thus, it is likely that *Alu*-mediated gene regulatory processes are
328 actively influencing mitonuclear gene expression, regulation, and protein function through
329 the pathways discussed above and reviewed in Chen and Yang (2017). Knowing this, the
330 dysregulation of epigenetic *Alu* regulatory pathways is a plausible source for mitochondrial
331 stress and dysfunction, with the CNS being particularly vulnerable (Larsen et al. 2017). Such
332 a mechanism could contribute to the initial activation of complex mitochondrial stress
333 pathways and incipient neuronal stress associated with sporadic neurologic disorders (e.g.,
334 inflammation, immune response, mitophagy, etc.). Importantly, these processes would
335 precede macroscopic pathologies such as protein aggregation and neuronal atrophy observed
336 in neurodegenerative diseases (Swerdlow et al. 2010; Larsen et al. 2017; Swerdlow 2017).
337 The *Alu* neurodegeneration hypothesis (*sensu* Larsen et al. 2017) proposes a 'double-
338 edged sword', whereby the beneficial *Alu*-related processes that underlie neuron diversity and
339 function also have the potential to disrupt mitochondrial homeostasis across neurological
340 networks through deleterious cascade events that are facilitated by eroding tissue-specific *Alu*
341 epigenetic control mechanisms. The stability of the brain's connectome and the entire CNS
342 depends on healthy mitochondrial populations within neurons, astrocytes, microglia and
343 supporting cells (Cai et al. 2011; Viader et al. 2011; Schwarz 2013; Jackson and Robinson
344 2017). Mitochondria play critical roles for a wide range of essential neuronal processes
345 including glucose and lipid metabolism, metal ion biosynthesis, cellular trafficking along
346 axons, neurotransmitter relay across synapses, and synaptic calcium homoeostasis (Schwarz
347 2013; Harbauer et al. 2014). Therefore, molecular mechanisms that are known to disrupt gene
348 expression and protein folding of genes that are essential for mitochondrial function can
349 ultimately disrupt neurological function.

350 Interference of mitochondrial dynamics across the CNS is consistently hypothesized
351 to occur during the earliest stages of mental, neurological, and neurodegenerative disorders
352 ranging from depression, epilepsy, and schizophrenia to ALS, AD, and Parkinson's disease
353 (PD; Lu 2009; Rezin et al. 2009; Kim et al. 2010; Coskun et al. 2012; Martin 2012;
354 Gottschalk et al. 2014; Larsen et al. 2017; Flippo and Strack 2017; Petschner et al. 2017).
355 Collectively, these disorders are estimated to impact approximately 250 million people
356 globally, accounting for at least 10.2% of the global disease burden (GBD 2015 Neurologic
357 Disorders Collaborator Group 2017). The occurrence of sporadic forms of human-specific
358 neurologic disorders (e.g. non-familial schizophrenia, ALS, late-onset AD, PD, etc.) across
359 the entire distribution of our species is suggestive of a common yet complex genetic
360 mechanism that evolved in primates and is amplified in humans (Larsen et al. 2017).
361 Considering this, we expand on the mitocentric view of idiopathic neurologic disease
362 manifestation by reviewing the evidence that unites primate-specific *Alu* activity with
363 incipient neurologic mitochondrial dysfunction.
364 Eukaryotic mitochondria are hypothesized to have originated from an endosymbiotic
365 alphaproteobacterium which, over expansive evolutionary time, evolved in parallel with host
366 genomes into the mitochondrial organelles that we observe today (Roger et al. 2017). The
367 human mitochondrial genome encodes only 13 proteins yet it is estimated that human
368 mitochondria depend on approximately ~2,000 genes encoded within the nuclear genome for
369 their functionality (Calvo et al. 2015; Johnson et al. 2017). These mitonuclear genes are thus
370 subject to deleterious *Alu* activity and *Alu*-related deleterious events have been linked to
371 many neurologic and neurodegenerative disorders, including epilepsy, Wilson's disease,
372 Leigh syndrome, PD, ALS, and AD (Table 1 and references therein; Figure 3). When
373 considering the incipient mitochondrial dysfunction observed across the spectrum of
374 neurological neurodegenerative disorders, it is possible that tissue-specific epigenetic

375 dysregulation of *Alu* elements within the CNS can ultimately manifest into distinct disease
376 phenotypes (Larsen et al. 2017).
377 Several interesting patterns emerge when examining the key neurologic processes that
378 are disrupted through deleterious *Alu* activity (Table 1). For example, mitochondria play an
379 essential role in maintaining intra-cellular metal ion homeostasis (e.g., iron, copper, and
380 zinc), the disruption of which can result in the increased production of free radicals that
381 damage mitochondria and contribute to the increased production of reduced oxygen species
382 (ROS; Rossi et al. 2004; Madsen and Gitlin 2007). The brain is especially sensitive to ROS
383 production, and iron, copper, and zinc-related oxidative stress has been linked to many
384 neurodegenerative disorders including AD, PD, and Wilson's disease (Rossi et al. 2004;
385 Madsen and Gitlin 2007). It is notable that deleterious *Alu* activity has been identified in
386 several genes that are essential to maintaining proper iron and copper homeostasis, including
387 *FXN*, *ATP7A*, *ATP7B*, *HMBS*, *NDUFS2*, *SLC30A6*, and *PARK7* (*DJ-1*) (Table 1; Gu et al.
388 2007; Kaler 2011; Girotto et al. 2014). Knowing this, it is possible that either global or tissue-
389 specific dysregulation of *Alu* elements within mitonuclear genes can alter mitochondrial
390 metal ion processing pathways thereby contributing to increased ROS production leading to
391 neurologic stress.
392 A second interesting pattern with respect to deleterious neurologic *Alu* activity
393 concerns metabolic pathways. The efficient processing of glucose and lipids across the CNS
394 is critical for the stability and function of neurons, and the disruption of mitochondrial-
395 mediated metabolic pathways has been linked to many neurologic disorders including AD
396 and peripheral neuropathies (Viader et al. 2013; De La Monte and Tong 2014). Deleterious
397 *Alu* activity occurs in genes that are critical for glucose and lipid metabolism, including
398 *ABCD1*, *ACAT1*, *ALMS1*, *APOB*, *GK*, *GLA*, *HPRT*, *LPL*, *PDHA1, PMM2*, *PSEN1, SOD2* and
399 *SPAST* (Table 1). Several of these genes encode for mitochondrial-related proteins that have

400 been implicated in metabolic diseases that directly, or indirectly, contribute to neurological
401 dysfunction. The connection between *Alu* elements and metabolic pathways is consistent with
402 the observation that *Alu* elements preferentially insert into metabolic genes, and this has led
403 to the hypothesis that *Alus* regulate the expression of genes related to Type 1 Diabetes
404 (Grover et al. 2003; Mirza et al. 2014; Kaur and Pociot 2015). Moreover, *Alu* RNAs act to
405 suppress the expression of both endothelial nitric oxide synthase (eNOS) and superoxide
406 dismutase 2 (SOD2) during hyperglycemic conditions (Wang et al. 2016), suggesting a
407 regulatory role of *Alu* elements during oxidative stress and strengthening the link between
408 *Alu* element activity and diabetes.

409 There is growing evidence linking sporadic AD with dysfunctional metabolic
410 pathways, leading some to consider AD as a 'Type 3 Diabetes' wherein glycolysis and lipid
411 homeostasis is altered (Steen et al. 2005; De La Monte et al. 2006; De La Monte and Wands
412 2008; De La Monte and Tong 2014; De Felice and Lourenco 2015; Mittal et al. 2016). The
413 most well-documented risk factor for AD is a variant within *APOE* (*APOE* ε4), a gene which
414 encodes for a glycoprotein that that mediates cholesterol and lipid transport (Saunders et al.
415 1993; Strittmatter et al. 1993; Mahley and Rall 2000). The *APOE* ε4 allele is strongly
416 associated with earlier onset of AD, and it is hypothesized that this is a result of the
417 disruption of cholesterol processing and subsequent accumulation of amyloid precursor
418 proteins (APP; i.e., the Amyloid cascade hypothesis). Although the 'Amyloid cascade
419 hypothesis' has dominated Alzheimer's research for decades (Hardy and Higgins 1992;
420 Selkoe 2000; McKhann et al. 2011), the failure of multiple drug trials targeting amyloid
421 pathways has led many in the Alzheimer's research community to search for alternative
422 hypotheses that can help explain the origin of neurodegenerative disease as well as novel
423 molecular pathways with therapeutic potential (Herrup 2015).

424 It is of particular interest then to note that a second genetic risk factor for AD,
425 *TOMM40*, is located immediately adjacent to *APOE* on human chromosome 19, and the two
426 genes are in tight linkage disequilibrium (Lyall et al. 2014; Roses et al. 2016a). *TOMM40*
427 encodes for a beta-barrel protein that ultimately forms a central pore in the outer
428 mitochondrial membrane (Shiota et al. 2015) and, much like *APOE*, genetic variants of
429 *TOMM40* are linked to cognitive impairment and neurodegenerative disease (Roses 2010;
430 Gottschalk et al. 2014; Greenbaum et al. 2014; Roses et al. 2016b; Arpawong et al. 2017).
431 The most-well known of these *TOMM40* variants is the rs10524523 (rs523) homopolymer
432 repeat, a variable stretch of deoxythymidine (T) located within *TOMM40* intron 6 (Roses
433 2010). The rs523 poly-T varies in length from approximately 12 to 46 nucleotides, and the
434 longer variants are statistically associated with thinning of the hippocampus (independent of
435 the *APOE* ε4 allele; Burggren et al. 2017) and earlier onset of AD (Lutz et al. 2010; Roses et
436 al. 2010). Interestingly, rs523 is embedded within tandemly repeated *Alu* elements and
437 originated from an *Alu* insertion event (Larsen et al. 2017). At least 149 *Alu* A-to-I editing
438 events are identified within *TOMM40*, the majority of which are associated with *Alu* elements
439 surrounding the rs523 repeat and intron 9 (Picardi et al. 2017a).
440 There is a potentially important link that unties *APOE* APP processing with the
441 functional mechanics of pre-protein transport through the TOMM pore. It is possible that
442 conformational changes of the Tom40 protein, potentially originating from *Alu*-mediated
443 events (see above, reviewed in Elbarbary et al. 2016; Chen and Yang 2017; Larsen et al.
444 2017), can ultimately serve to restrict the passage of lipids across the outer-mitochondrial
445 membrane (Larsen et al. 2017). When combined with altered APP processing, this process
446 could account for the initial site of intra-cellular protein accumulation that is hypothesized to
447 precede extra-cellular plaque formation during very early stages of AD (Skovronsky et al.
448 1998; D'Andrea et al. 2001; Takahashi et al. 2002). Consistent with this hypothesis is the

449 direct observation of APP accumulation at the TOMM pore (Devi et al. 2006) as well as
450 functional tolerance of Tom40 conformational changes by mitochondria (Mager et al. 2011;
451 Kuszak et al. 2015). Importantly, this mechanism could help to explain the common patterns
452 of protein accumulation (e.g., amyloid plaques and alpha-synuclein Lewy bodies) observed
453 across the spectrum of neurodegenerative disease, including ALS, AD, and PD (Ross and
454 Poirier 2004; Gottschalk et al. 2014; Larsen et al. 2017). An age or stress-related component
455 to Tom40 conformational changes comes with the epigenetic dysregulation of *Alu* elements
456 associated with the aging process or traumatic stress (see Larsen et al. 2017). Whether or not
457 these processes are directly mediated by deleterious *Alu* events remains to be tested, however,
458 it is notable that *Alu* exons and *Alu* somatic retrotransposition events have been identified in
459 several TOM genes that are required for the stability of the translocase of the outer
460 mitochondrial membrane and pre-protein import, including *TOMM5*, *TOMM7*, *TOMM22*,
461 *TOMM40*, and *TOMM40L* (Baillie et al. 2011; de Andrade et al. 2011; Lin et al. 2016).
462 With respect to *Alu* elements, mitochondrial dysfunction, and the broader pathological
463 scope of AD and other neurodegenerative diseases, there is evidence suggesting that *Alu*-
464 derived peptides interact with tau proteins, perhaps serving a regulatory role for tau
465 phosphorylation (Hoenicka et al. 2002). Tau is a microtubule associated protein that
466 functions to stabilize axonal microtubules and to transport mitochondria along axons, and
467 taupathies (including tau hyperphosphorylation) are a characteristic feature of several
468 neurodegenerative diseases including AD, progressive supranuclear palsy, corticobasal
469 degeneration, and Pick's disease (Ittner and Götz 2011; Khanna et al. 2016). The *MAPT* gene
470 encodes for tau and alternative splicing events of *MAPT* result in multiple tau isoforms
471 (Reddy 2011). Approximately 86 *Alu* elements (including FLAMs) are distributed throughout
472 *MAPT* introns and A-to-I editing is occurring at 315 *Alu* related sites with elevated levels at
473 the 3' end of *MAPT* (REDIportal database; Picardi et al. 2017a). When considering the

474 potential for *Alu* structural variants of *MAPT* (including DNA and pre-mRNA secondary
475 structures) and evidence of *Alu* RNAs interacting with tau proteins (Hoenicka et al. 2002), we
476 recommend additional studies aimed at elucidating the regulatory impacts that *Alu* elements
477 might have on *MAPT* gene expression and tau phosphorylation.
478
479 **A-to-I editing and the potential for mitochondrial stress**
480 Although several neurological disorders are hypothesized to be the result of disruptive
481 A-to-I editing processes across the CNS (see above), it is presently unknown whether or not
482 these processes are actively influencing mitochondrial function. What evidence is there
483 indicating that post-transcriptional modification of mitonuclear genes can alter gene
484 expression or function? Are there particular neurological or neurodegenerative disorders that
485 are associated with mitonuclear genes that have elevated levels of A-to-I editing? To provide
486 insights into these questions, we searched the REDIportal A-to-I editing database (Picardi et
487 al. 2017a) for mitonuclear genes where 1) A-to-I editing has been identified within *Alu*
488 elements in coding regions and 2) A-to-I editing has contributed to non-synonymous amino
489 acid changes. We identified 57 mitonuclear genes with A-to-I editing occurring within
490 putative *Alu* exons and in 52 of these genes the post-transcriptional modification resulted in
491 nonsynonymous amino acid changes (Supplementary Table 1). Many of these genes are
492 involved with essential neuronal processes including calcium binding and transport, zinc
493 transport, apoptosis regulation, voltage-gated ion channels, and mitochondrial elongation
494 with notable examples including *ADSL*, *BAX*, *CASP2*, *COQ2*, *DFFB*, *FBXO18*, *LYRM4*,
495 *PACRG*, and *SLC30A6* (Supplementary Table 1).
496 From a broader perspective, we identified enhanced A-to-I editing across 134
497 mitonuclear genes that are associated with a spectrum of neurologic and neurodegenerative
498 disorders ranging from depression, tobacco use disorder, and bipolar disorder to ALS, Leigh

499 syndrome, PD, and AD (Supplementary Table 2). In light of these patterns, we hypothesize
500 that system-wide or tissue-specific epigenetic dysregulation of *Alu* A-to-I editing within the
501 CNS can serve to disrupt key mitochondrial biochemical processes, thus potentially
502 contributing to incipient mitochondrial and neuronal stress (Figure 3).
503
504 **Conclusions**
505 Enhanced somatic retrotransposon throughout neurogenesis contributes to the mosaic
506 brain, however, such activity likely contributes to mosaic pathways leading to disease (Erwin
507 et al. 2014). Elucidating these pathways might ultimately provide insight into the sporadic
508 nature of idiopathic diseases that are impacting the global human population. The disruption
509 of *Alu*-mediated pathways that underlie gene regulation is a plausible mechanism for the
510 origin of complex human-specific neurologic and neurodegenerative disorders. Although
511 many of these disorders have similar phenotypes (e.g., mitochondrial dysfunction), it is
512 possible that these phenotypes arise from deleterious activity operating across tissue-specific
513 gene networks. If correlated with eroding or fluctuating epigenetic control mechanisms of
514 retrotransposons that are associated with aging, cellular senescence, and/or cellular stress
515 (Belancio et al. 2010; Pal and Tyler 2016; Schneider et al. 2017), then such mechanisms
516 might largely escape purifying selection and would be difficult to detect using traditional
517 methods (e.g., genome-wide association studies). It is important to note that the *Alu*-centric
518 mechanisms discussed herein collectively provide a unified framework for multiple
519 hypotheses that have been put forth regarding the origin of neurodegenerative disease
520 including inflammation, oxidative-stress, metabolic dysfunction, and accumulation of protein
521 bodies (see above).
522 *Alu* elements have played a pivotal role in the evolution of the human epigenome
523 (Prendergast et al. 2014), and both hyper- and hypomethylation of *Alu* elements have been

correlated with a number of age-related disorders including Alzheimer's disease, multiple sclerosis, osteoporosis, and many forms of cancer (Bollati et al. 2009; Jintaridth and Mutirangura 2010; Belancio et al. 2010; Jintaridth et al. 2013; Neven et al. 2016). In light of these patterns, as well as the newly discovered regulatory roles of *Alu* elements (Polak and Domany 2006; Chen and Carmichael 2008; Chen and Yang 2017), we recommend additional research that focuses on the epigenetic interplay between *Alu* elements and mitochondrial gene networks in the central nervous system.

Acknowledgments

We thank A.D. Brown, W.K. Gottschalk, and M. Mihovilovic for helpful discussion. C. Hohoff, B. Ciapa, and an anonymous reviewer kindly reviewed the manuscript and provided helpful comments. This is Duke Lemur Center publication number 1389.

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1137 **Figure Legends**

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1139 **Figure 1.** Select mechanisms whereby *Alu* elements can alter gene expression and function

1140 (also see Elbarbary et al. 2016). **A:** Sequence homology and orientation of *Alu* elements

1141 contributes to the formation of distinct secondary structures in both DNA and RNA. DNA

1142 *Alu* G-quadruplex structures can alter transcription kinetics (Varizhuk et al. 2016) and pre-

1143 mRNA *Alu* binding forms stem-loop structures that are the primary site for A-to-I editing

1144 (see Figure 2). **B:** Recombination of intra-gene *Alu* elements resulting in exon deletion. **C:**

1145 Exonification of intronic *Alus* contributing to the production of alternative mRNAs. **D:**

1146 Environmental or traumatic stress cascades resulting in increased expression of *Alu* RNAs

1147 that contribute to inflammation (Li and Schmid 2001; Tarallo et al. 2012; Hunter et al. 2015;
1148 Lapp et al. 2016), the disruption of global gene transcription through Pol II binding (Mariner
1149 et al. 2008), and an increase of H3K9 histone methylation that alters *Alu* epigenetic pathways
1150 (Varshney et al. 2015; Lapp and Hunter 2016; Larsen et al. 2017).
1151
1152 **Figure 2.** Intronic *Alu* elements located in close proximity (**A**) can bind to each other within
1153 pre-mRNAs (**B**) thereby producing a stable stem-loop secondary structure that is the primary
1154 substrate for A-to-I editing in primates. ADAR proteins bind to pre-mRNA *Alu* structures
1155 (**C**) and convert adenosine residues to inosine. If occurring in coding regions, the translation
1156 machinery then interprets the inosine residues as guanosine and this can contribute to amino
1157 acid changes and alternative protein conformations (**D**).
1158
1159 **Figure 3.** Deleterious *Alu* activity operating on mitonuclear genes can disrupt mitochondrial
1160 function in the CNS and contribute to a number of diseased phenotypes (see Table 1). The
1161 type and severity of associated neurological and neurodegenerative disorders depends on the
1162 deleterious *Alu* mechanism of action, the mitonuclear gene pathways involved, the time or
1163 developmental stage of induction, level or severity of traumatic stress, and tissue specificity
1164 (see Larsen et al. 2017). If operating across the suite of mitonuclear genes through epigenetic
1165 pathways, the mechanism helps to explain the origin of incipient mitochondrial stress and
1166 CNS connectome destabilization that is observed across the spectrum of neurological and
1167 neurodegenerative disorders.
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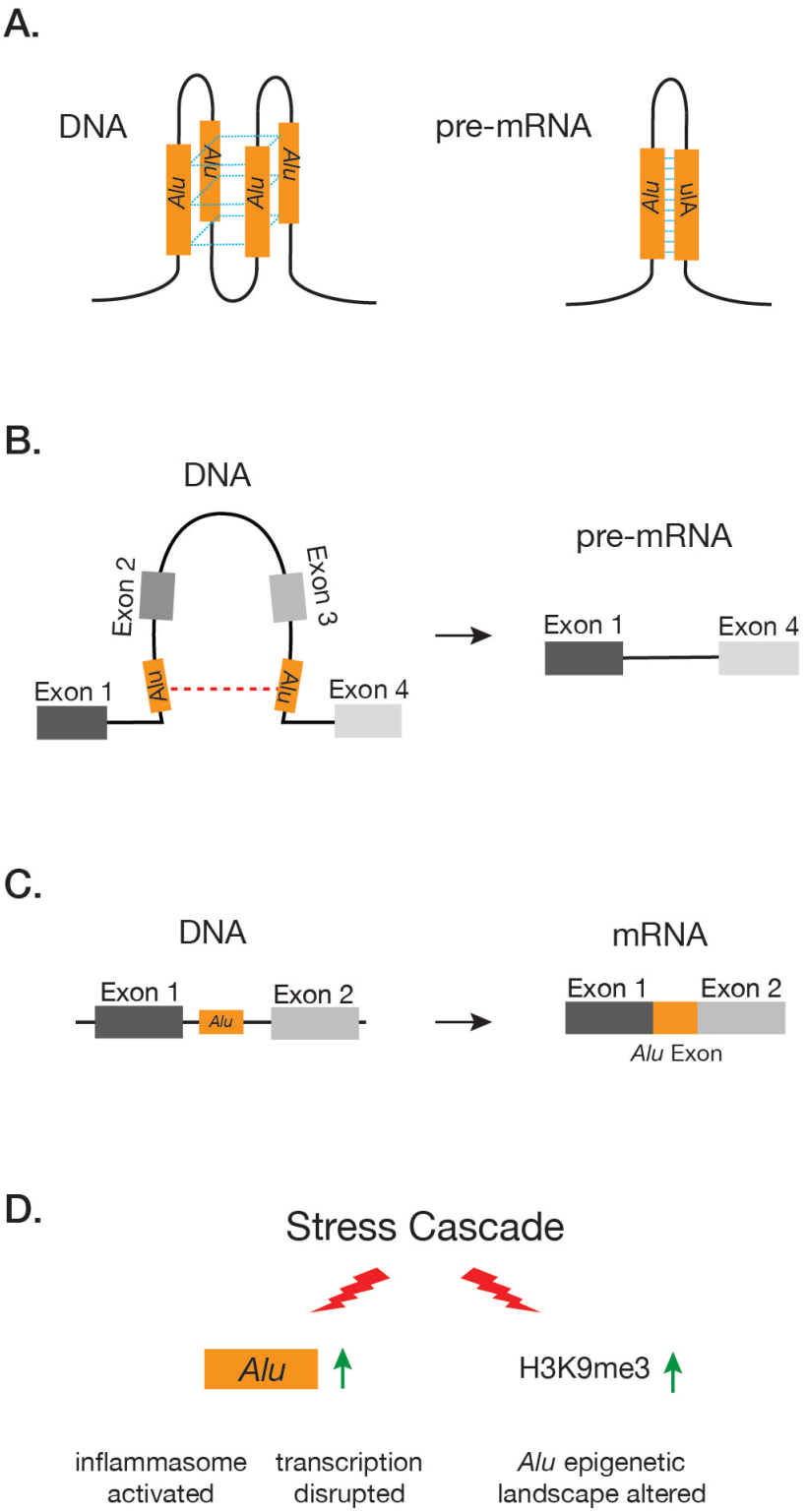
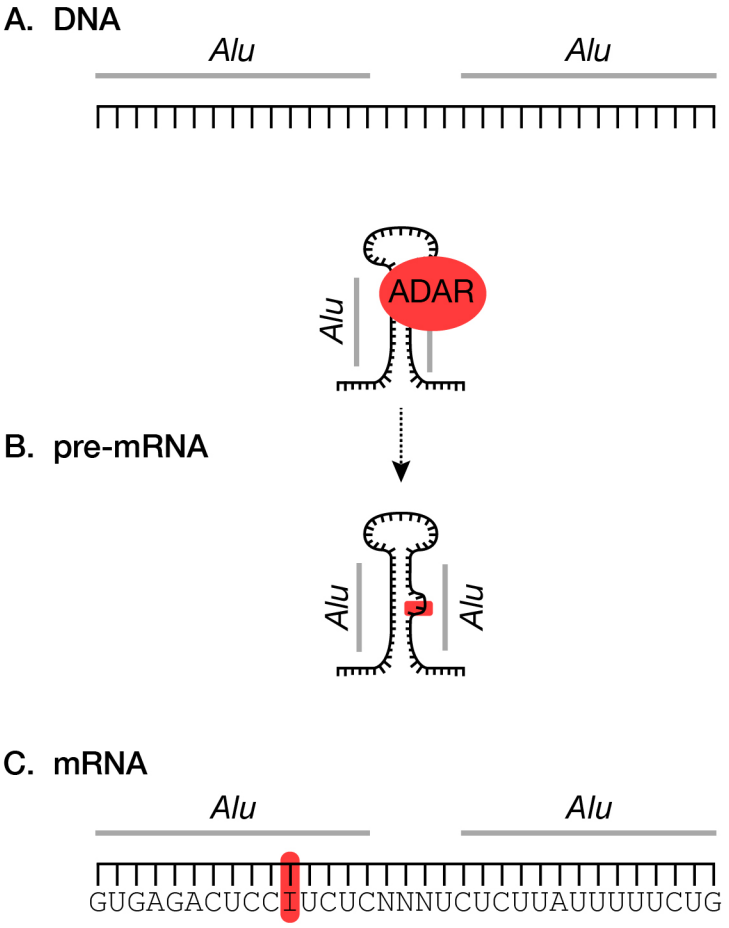

A.
DNA
Alu
Alu
Alu
Alu
pre-mRNA
Alu
Alu
B.
DNA
Exon 2
Exon 3
Exon 1
Alu
Alu
Exon 4
pre-mRNA
Exon 1
Exon 4
C.
DNA
Exon 1
Alu
Exon 2
mRNA
Exon 1
Exon 2
Alu Exon
D.
Stress Cascade
Alu
H3K9me3
inflammasome activated
transcription disrupted
Alu epigenetic landscape altered

Figure 1.

1176



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1179 **Figure 2.**

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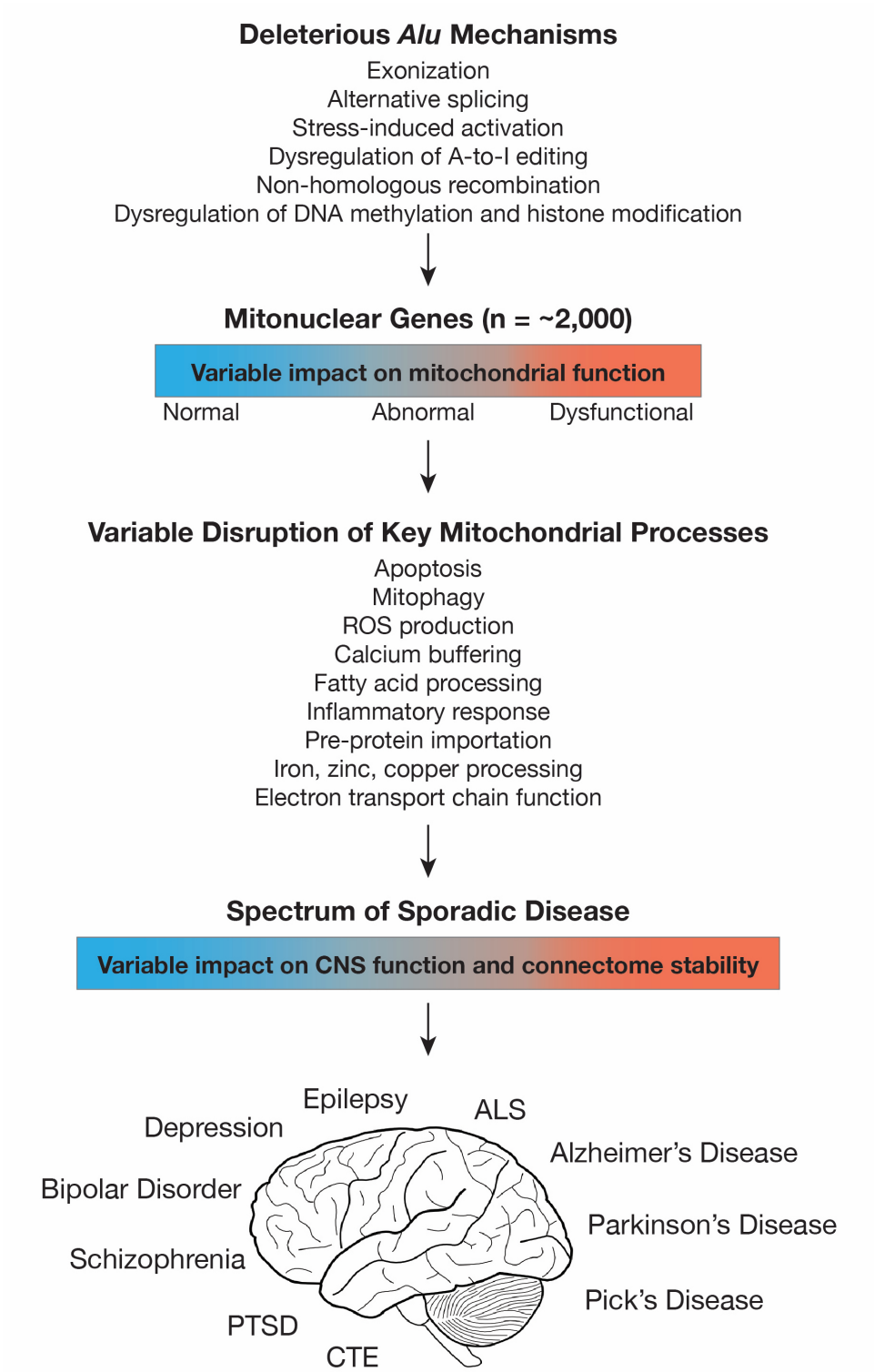
Deleterious *Alu* Mechanisms
Exonization
Alternative splicing
Stress-induced activation
Dysregulation of A-to-I editing
Non-homologous recombination
Dysregulation of DNA methylation and histone modification
Mitonuclear Genes (n = ~2,000)
Variable impact on mitochondrial function
Normal
Abnormal
Dysfunctional
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
Parkinson's Disease
Schizophrenia
Pick's Disease
PTSD
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