J Bioenerg Biomembr (2009) 41:411–416
DOI 10.1007/s10863-009-9239-1

# Is there a primary role of the mitochondrial genome in Alzheimer's disease?

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Published online: 2 October 2009


**Abstract** The "mitochondrial cascade hypothesis" could explain many of the biochemical, genetic and pathological features of sporadic Alzheimer's disease (AD). Somatic mutations in mitochondrial DNA (mtDNA) could cause energy failure, increased oxidative stress and accumulation of amyloid β, which in a vicious cycle reinforces mtDNA damage and oxidative stress. Despite the evidence of mitochondrial dysfunction in AD, and despite the cognitive impairment frequently reported in patients with mtDNA mutation, no causative mutation in the mtDNA have been linked to AD. Indeed, results of studies on the role of mtDNA polymorphisms or haplogroups in AD are controversial. In this minireview, we summarize the actual knowledge about the involvement of mtDNA in AD pathology.

**Keywords** Alzheimer · mtDNA · Oxidative stress

## Introduction

Mitochondria are dynamic and pleomorphic organelles, composed of a smooth outer membrane surrounding an inner membrane of significantly larger surface area that, in turn, surrounds a protein-rich core, the matrix. They contain two to ten molecules of DNA, the mitochondrial DNA (mtDNA) (DiMauro and Schon 2003).

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The mtDNA is a 16.5-kb circular minichromosome built up of complementary H- and L-strands (DiMauro and Schon 2003). The mitochondrial genome contains 37 genes, 13 of which encode for subunits of electron transport chain (ETC) complexes, 22 for transfer RNAs (tRNAs), and two for ribosomal RNAs (rRNAs) (DiMauro and Schon 2003). The 13 mtDNA-encoded polypeptides are part of the respiratory system and are assembled together with nuclear-encoded subunits. Seven of them belong to complex I or NADH dehydrogenase, NADH:ubiquinone oxidoreductase (ND1, ND2, ND3, ND4, ND4L, ND5, ND6), one to complex III or ubiquinol: ferricytochrome *c*-oxidoreductase, three to complex IV or cyt *c* oxidase (COX I, COX II and COX III) and two to complex V or ATP synthase (ATPase6 and ATPase8). The remaining mitochondrial proteins, including all the subunits of complex II, are encoded by nuclear DNA (nDNA). The mitochondrial chromosome is not protected by histones, its mutation rate is 10 times higher than nDNA, and it does not undergo recombination during meiosis (Cantuti-Castelvetri et al. 2005). The mitochondrial genome is maternally inherited. MtDNA mutations are classified as either large-scale rearrangements (partial deletions or duplications), usually sporadic, or point mutations, which are usually maternally inherited, and concern genes responsible for protein synthesis (rRNAs or tRNAs), or genes encoding subunits of the ETC (Filosto and Mancuso 2007). The phenotypic expression of mtDNA mutations depends on the affected gene, its tissue distribution and the different dependency of different organs and tissues on the mitochondrial energy supply. Visual and auditory pathways, heart, central nervous system (CNS) and skeletal muscle are the tissues mostly involved, because of their dependence on aerobic energy production (DiMauro and Schon 2003). The involvement of CNS may express with epilepsy, stroke-

like episodes, ataxia, spasticity and dementia. Cognitive functions and intellectual abilities may decline from initially focal cognitive impairment to dementia (Finsterer 2008; Nishioka et al. 2008). However, little is known about whether pathogenic mtDNA mutations and the resultant mitochondrial respiration deficiencies contribute to the expression of cognitive alterations, such as impairments of learning and memory.

Mitochondria play a central role in apoptotic cell death, and mitochondrial dysfunction appears to have a certain impact on the pathogenesis of several neurodegenerative disorders, such as Alzheimer's Disease (AD) (Mancuso et al. 2008b). AD is associated with progressive and irreversible loss of neurons, particularly in the cortex and hippocampus, extracellular senile plaques containing aggregated amyloid beta (Aβ), and neurofibrillary tangles composed of the hyperphosphorylated form of the microtubular protein tau (Selkoe 2001). Most forms of AD develop after the age of 65 and are considered to be sporadic because they lack an obvious familial aggregation. The meaning of the term "sporadic" has, however, been gradually modified by the concept of non-Mendelian (complex) transmission because there is no longer doubt that also the common sporadic late-onset form of AD involves a strong genetic predisposition.. To date, the major risk factor in sporadic AD is recognized in the allele ε4 of apolipoprotein E (*ApoE4*). The Aβ cascade hypothesis remains the main pathogenetic model of familial AD with mutation in amyloid precursor protein (*APP*) and presenilin genes (Hardy and Selkoe 2002), but its role in the majority of sporadic AD cases without mutations in these genes (accounting for the great majority of AD cases) and the exact mechanism of its neurotoxicity are still unclear. Combination of multiple genetic studies and physiopathological data indicate that whereas familial, early-onset forms of AD are mainly linked to genes that are involved in Aβ overproduction, genetic variants of apolipoprotein E and other defined loci may influence susceptibility to late-onset forms of the disease via a role in Aβ clearance and\or Aβ toxicity. In this contest, the role of the mitochondrion and of its genome (which is highly polymorphic) is still matter of debate. Several lines of evidence suggest that Aβ exerts its toxicity intracellularly (Gouras 2000; Wirths et al. 2004), pointing to a role of the mitochondrion in this process (Wang et al. 2007). Morphological, biochemical and genetic abnormalities of the mitochondria in several AD tissues have been reported. Impaired mitochondrial respiration, particularly COX (complex V) deficiency, has been observed in brain, platelets and fibroblasts of AD patients (Mancuso et al. 2008b). Also abnormal mitochondrial dynamics may be a common pathway leading to mitochondrial and neuronal dysfunction critical to the pathogenesis of AD (Wang et al. 2009b). Somatic mutations in mtDNA could cause energy failure, increased oxidative stress and accumulation of Aβ, which in a vicious cycle reinforces mtDNA damage and oxidative stress (Fig. 1). However, despite the evidence of mitochondrial dysfunction in AD, and despite the cognitive impairment frequently reported in patients with mtDNA mutation, no causative mutations in the mtDNA have been linked to AD so far.

Should we hypothesize a primary role of the mtDNA in the degenerative cascade leading to AD? Here, we review the actual knowledge about the involvement of mtDNA in AD pathology.

## The "cybrid" model of Alzheimer's disease

Cell depleted from endogenous mtDNA have been repopulated with mitochondria (with their own mtDNA) from AD patients and normal controls, creating cytoplasmic hybrid cells (or "cybrids"), in order to explain the origin of the bioenergetic deficits in AD (King and Attardi 1989). This application showed that the enzymatic defects can be transferred to mtDNA-deficient cells, thus implicating mtDNA alterations (Swerdlow et al. 1997). AD cybrids showed also overproduction of amyloidogenic Aβ peptides (1–40, 1–42), accumulation of amyloid deposits similar to amyloid plaques seen in AD brains, as well as major vulnerability to apoptosis (Khan et al. 2000). The worsening of the bioenergetic impairment occurred in long-term culture (Trimmer et al. 2004). Not every study with cybrid cells detected differences between AD patients and controls (Ito et al. 1999). Nevertheless, the majority of these studies demonstrated that cybrid cells and cerebral tissue in sporadic AD have similar morphological and biochemical phenotype, according to the hypothesis that mtDNA changes might be involved in the pathogenesis of sporadic AD (Mancuso et al. 2008b).

## MtDNA damage in AD patients

In AD brains, endothelial cells of vessels with atherosclerotic lesions and nearby perivascular cells have been reported to contain clusters of normal and deleted mitochondrial genomes (Aliev et al. 2003). Chronic hypoperfusion may be an element involved in the pathogenesis of AD, triggering oxidative stress and mitochondrial dysfunction (Aliev et al. 2008). Aging and cerebrovascular comorbidity may impair cerebral perfusion, subsequently inducing brain capillary degeneration and suboptimal delivery of energy substrates to neuronal tissue (De la Torre 2002). Mitochondrial dysfunction, oxidative stress, decreased ATP production and increased calcium entry,

abnormal protein synthesis, cell ionic pump deficiency, signal transduction defects, and neurotransmission failure resulting from hypoperfusion may contribute to the progressive cognitive decline characteristic of AD and neurodegeneration (Aliev et al. 2003, 2005).

Clusters of mitochondria-derived lysosomes and necrotic changes have been detected in endothelial and perivascular cells of human AD brain microvessels (Moreira et al. 2007). In AD brain microvessels, but not in age-matched control brains, mtDNA deletions have been reported, identified by ultrastructural evaluations with probes for human normal and 5-kB deleted mtDNA (Moreira et al. 2007). Immunocytochemical analysis demonstrated that the mitochondrial abnormalities in neurons were associated with increased markers of lipid peroxidation (Moreira et al. 2007). An hypothetical sequence of events for AD progression may go from oxidative damage (protein nitration, lipid peroxidation, nDNA and mtDNA damage, RNA oxidation) to the formation of pre-neurofibrillary tangles inducing irreversible neuronal damage (Aliev et al. 2008).

Increased levels of 8-hydroxyguanosine (8-OHG), index of mtDNA damage, have been reported in the hippocampus and cerebral neocortex in AD, but not in the cerebellum (Nunomura et al. 1999). Interestingly, 8-OHG levels were inversely related to the amount of intracellular oligomeric forms of Aβ, suggesting a complex interplay between ROS and Aβ (Nunomura et al. 2004). MtDNA resulted to have approximately 10-fold higher levels of oxidized bases than nDNA, that guanine is the most vulnerable base to DNA damage, and that multiple oxidized bases are significantly higher in AD brain specimens in comparison to controls (Wang et al. 2005).

Oxidative DNA damage is repaired either in nuclei and in mitochondria by the DNA base excision repair (BER) process (Altieri et al. 2008). Mitochondria have an independent BER machinery, characterized by a sequence of polymerase and ligase, whose reduction in functionality has been reported in brains of patients with AD, resulting in elevated levels of unrepaired mtDNA (Fishel et al. 2007).

On the basis of the "cybrid" model of AD, and of the reported damage of mtDNA in AD patients, it has been speculated that aging-related mtDNA mutations may result in impaired energy production, increased amount of ROS and cell damage, and subsequently neurodegeneration and AD pathology (see Fig. 1).

## Mitochondrial DNA mutations in AD

To evaluate the contribution of mtDNA polymorphism or rare variants, or both of them, to the aetiology of late-onset AD, Tanaka and co-workers analyzed complete mtDNA from blood of 153 AD patients and 129 normal control subjects. The results of this study showed that inherited mtDNA common polymorphisms could not be the single major causes of AD, but that some rare variants in the protein-coding region may have protective effects for high-risk populations with the *APOE4* allele (Tanaka et al. 2009). Moreover, this study supported the hypothesis that the np956-965 poly-C insertion and 856A>G variant might be a risk factor for AD (Tanaka et al. 2009). In a recent study involving a total of 236 subjects (71 AD patients, 84 patients with mild cognitive impairment –MCI-, 41 cognitively normal aging controls, and 40 young controls), heteroplasmy of mitochondrial D310 mononucleotide repeat region in blood samples has been evaluated (Wang et al. 2009a). In AD patients heteroplasmy of the mtDNA D310 polycytosine repeat region resulted significantly more frequent than in the other groups of subjects, and insertion of cytosine was the most common mutation type (Wang et al. 2009a). MCI patients did not harbor a significantly

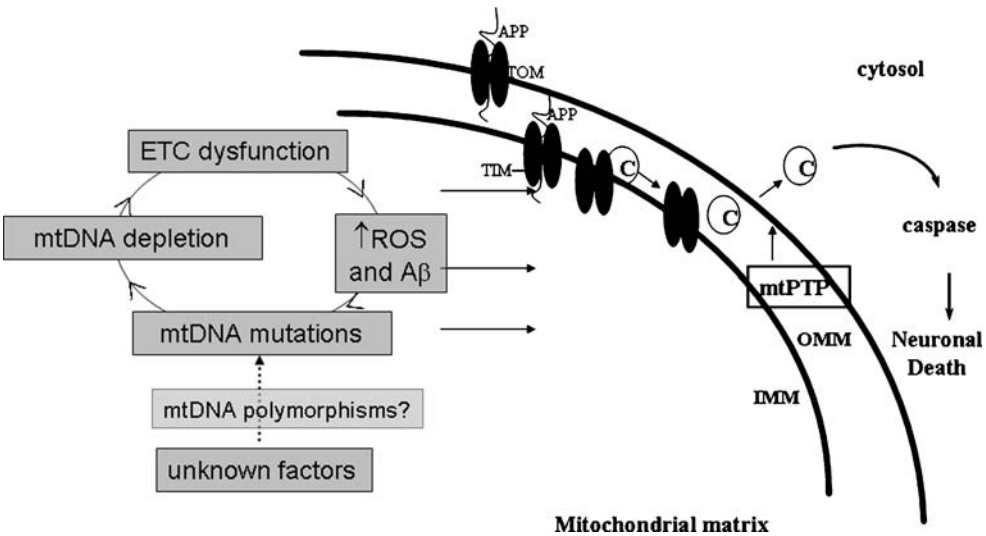


**Fig. 1** A proposed mechanism of mitochondrial induced cell death in Alzheimer's disease. Legend: *Aβ* amyloid-β; *ROS* reactive oxygen species; *ETC* electron transport chain; *mtPTP* mitochondrial permeability transition pore; *C* cytochrome c; *IMM* inner mitochondrial membrane; *OMM* outer mitochondrial membrane; *APP* amyloid precursor protein; *TOM* and *TIM* protein importation translocases of the mitochondrial outer and inner membranes. For further details, see text. (*Modified from Mancuso M et al., Antioxid Redox Signal 2007;9:1631–1646*)

higher rate of heteroplasmy in D310 than cognitively normal elderly subjects (Wang et al. 2009a). An increase of somatic mtDNA rearrangements has been observed also in AD brains. The mtDNA "common deletion" has been reported to be elevated about 15-fold in AD brains (Corral-Debrinski et al. 1994). Furthermore, the mtDNA A4336G transition was observed more frequently in AD patients (Shoffner et al. 1993).

More recently, mtDNA control region (CR) mutations have been reported as more frequent in AD brains than in controls (Coskun et al. 2004). In particular, two heteroplasmic changes were specific for AD brains (T414C and T477C) (Coskun et al. 2004). 65% of the AD brains harboured the T414G mutation, whereas this mutation was absent from in all control samples (Coskun et al. 2004). The mtDNA CR from patients and control brains has been cloned and sequenced. AD brains had an average 63% increase in heteroplasmic mtDNA CR mutations (and 130% increase in patients older than 80 years) (Coskun et al. 2004). These mutations preferentially altered known mtDNA regulatory elements. Furthermore, the AD brains showed an average 50% reduction in mtDNA content and in the ND6 complex I transcript, which may reduce the mitochondrial oxidative phosphorylation (Coskun et al. 2004).

On the other hand, another study involving a larger number of tissue samples did not identify the T414C mutation in AD brains (Chinnery et al. 2001). Elson and co-workers sequenced the complete coding regions of 145 autoptic AD brain samples and 128 normal controls, and observed that for both synonymous and non-silent changes the overall numbers of nucleotide substitutions were the same for the AD and control sequences (Elson et al. 2006). In conclusion, no surely causative mtDNA mutations have been reported in AD patients.

## Mitochondrial haplogroups and Alzheimer's disease

The identification of a possible role for mitochondrial genomic dysfunction in AD, and at the same time the unsuccessful research for mtDNA mutations in AD patients (Elson et al. 2006), encouraged to study polymorphisms, or clusters of polymorphisms, in mtDNA of AD patients. Polymorphisms in mtDNA may cause differences in the encoded proteins, resulting in changes in respiratory chain activity and increasing free radicals. This may result in a predisposition, for an individual or a population with the same polymorphism, to develop early apoptotic processes, accumulation of mitochondrial damages and somatic DNA mutations (Mancuso et al. 2008a). In mice, mtDNA polymorphism seem to be involved in cognitive functioning (Roubertoux et al. 2003).

The basal branching structure of mtDNA variation in most parts of the world is now well understood (Torroni et al. 2006) African haplogroups fall into seven major families (L0, L1, L2, L3, L4, L5, L6). About 85 thousand years ago, probably in the Horn of Africa, the root of haplogroup L3 gave rise to many descendant haplogroups (probably because of some colonization event or local population growth). Non-African mtDNA descend from L3 and belong either to the M or N superclades. In the Indian subcontinent and in Southeast Asia there is the richest basal variation in the three originated by haplogroups M and N, and this suggests a rapid colonization along the southern coast of Asia, about 60 thousand years ago (Torroni et al. 2006). The expansions northwords occurred later, about 45 thousand years ago. Over 30 subclades of the haplogroup M are present in Asia. Haplogroups A, B, C, D and X have been found in the Americas, coming mainly from Asia. In Europeans and Near Easterners (who share a rather recent common ancestor) nine different mitochondrial haplogroups have been identified (H, I, J, K, T, U, V, W, X). The variation in the basal European mtDNA haplogroups dates to about 45,000 years ago. Complete mtDNA sequencing and the increasing number of samples analyzed allow subdividing haplogroups in smaller groups identifying younger branches on the mtDNA evolution tree; sub-haplogroups classification is continuously evolving (Torroni et al. 2006).

Specific mitochondrial haplogroups have been linked to longevity (Bilal et al. 2008). Therefore, if they can be associated with longevity, mitochondrial haplogroups may be involved in the genesis of the opposite spectrum of longevity and life, neurodegeneration and death.

Multiple independent studies obtained contrasting results. Chagnon and co-workers (Chagnon et al. 1999) reported that haplogroups T was under-represented in AD patients, and that haplogroups J over-represented. Van der Walt and co-workers reported that haplogroup U in males was related to a significant increase in risk of developing AD, while in females seemed to be associated to a significant protection (Van der Walt et al. 2004). In an Italian sample of subject, instead, haplogroups K and U had a lower frequency in apolipoprotein (Apo) *E4* carriers, whereas in control subjects this correlation was not present (Carrieri et al. 2001). Therefore, haplogroups K and U may play a role in neutralizing the effect of the major known AD risk factor *E4* allele (Carrieri et al. 2001).

Very recently, Maruszak and co-workers (Maruszak et al. 2008) evaluated the involvement of mitochondrial haplogroups, haplogroup clusters (HV, UK, TJ, IWX) and of two functional mtDNA single nucleotide polymorphism (mtSNPs 4216 and 4917) in the pathogenesis of AD in the Polish population. These authors observed that HV cluster seemed to be significantly associated with the risk of AD, regardless of the ApoE4 status (Maruszak et al. 2008). The

same study reported no evidence for the involvement of haplogroup U, K, J or T in AD risk (Maruszak et al. 2008). Two studies including only neuropathologically proven cases of AD of European descent indicated that mtDNA haplogroups were not associated with AD (Elson et al. 2006; Chinnery et al. 2000).

A study performed in our laboratory investigated the frequency of the common European mtDNA haplogroups in a clinically well defined group of 209 unrelated patients and 191 controls, both with clear Tuscan origin, in order to minimize the risk of false associations between gene markers and disease (Mancuso et al. 2007). The frequency of haplogroups H, I, J, K, T, U, V, W and X was not significantly different between patient and control groups, without significant difference between genders (Mancuso et al. 2007). *ApoE4* allele was significantly more frequent in patients than in controls, and was not associated with any haplogroup (Mancuso et al. 2007). Our data also excluded any possible association between mtDNA haplogroups, age of onset and mean survival (Mancuso et al. 2007).

## Conclusion

Although AD is the most common cause of dementia in the elderly, its aetiology is still not fully understood. The aetiology of AD is complex, and only a minority of cases appears to be primarily genetic. Mitochondria seem to play a crucial role in the development of this disease. Furthermore, the majority of cybrid studies demonstrated similar morphological and biochemical phenotype between cybrid cells and cerebral tissue in sporadic AD, supporting the hypothesis that mtDNA changes might be involved in the mitochondrial impairment of sporadic AD. However, despite the cybrid data and although morphological, biochemical and molecular abnormalities have been clearly reported in AD brain, the role of the mitochondrial genome and of its haplogroups as a risk factor is still controversial. To date, no surely causative mtDNA mutations have been discovered in AD patients. Furthermore, studies attempting to identify mtDNA mutations in brains of AD patients obtained controversial results. The mtDNA alterations that cybrid models induce to hypothesize might be due to somatic factors, i.e. cronic hypoperfusion and oxidative damage (Mancuso et al. 2009).

Most likely, the mtDNA do not play a primary role, and, therefore, it should be involved subsequently (see Fig. 1). Indeed, the APP "stocked" in the TOM transporters and the altered mitochondrial dynamics seem pivotal, able to cause mitochondrial impairment, respiratory deficiency and oxidative stress (Mancuso et al. 2009).

It will be important to develop a better understanding of the role of oxidative stress and mitochondrial energy metabolism in AD, and its link with the amyloid hypothesis in aging and AD, since it may lead to the development of more effective treatment strategies for this devastating disorder (Mancuso et al. 2009).

**Acknowledgements** This work was performed in the frame of AMBISEN Center, High Technology Center for the study of the Environmental Damage of Endocrine and Nervous System, University of Pisa.

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