Review Article

May "Mitochondrial Eve" and Mitochondrial Haplogroups Play a Role in Neurodegeneration and Alzheimer's Disease?

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Mitochondria, the powerhouse of the cell, play a critical role in several metabolic processes and apoptotic pathways. Multiple evidences suggest that mitochondria may be crucial in ageing-related neurodegenerative diseases. Moreover, mitochondrial haplogroups have been linked to multiple area of medicine, from normal ageing to diseases, including neurodegeneration. Polymorphisms within the mitochondrial genome might lead to impaired energy generation and to increased amount of reactive oxygen species, having either susceptibility or protective role in several diseases. Here, we highlight the role of the mitochondrial haplogroups in the pathogenetic cascade leading to diseases, with special attention to Alzheimer's disease.

1. Introduction

The mitochondrion is a membrane-enclosed cytoplasmic organelle, which has evolved from a primitive aerobic bacteria by means of a symbiotic relationship that started 1.5 billions years ago [1]. These organelles range from 0.5 to 10 micrometers (μm) in diameter and are composed of compartments devoted to specific functions. These regions include the outer membrane, the intermembrane space, the inner membrane, the cristae, and the matrix. Mitochondria are described as "cellular power plants" because they produce most of the cell's supply of adenosine triphosphate (ATP) [2], by means of the oxidative phosphorylation (OXPHOS) machinery, which comprises electron transport chain (ETC) and ATP synthase (complex V). The ETC provides the cell with the most efficient energetic outcome in terms of ATP production. It consists of four multimeric protein complexes (complex I to IV) located in the inner mitochondrial membrane together with complex V [3].

Furthermore, mitochondria are key regulators of cell survival and death. ETC dysfunction leads to reduced ATP production, impaired calcium buffering, and increased generation of reactive oxygen species (ROS) [4]. Mitochondria

have their own DNA, the mitochondrial DNA (mtDNA), represented by a circular molecule of 16.5 kb without introns, constituting of a heavy chain (H) and a light chain (L) [3, 5]. mtDNA carries 37 genes: 22 encoding for mitochondrial transfer RNAs (tRNAs) (for the 20 standard amino acids, plus an extra gene for leucine and serine), 2 for ribosomal RNAs (rRNAs) and 13 encoding for polypeptides subunits of complexes of the respiratory chain system, 7 of them belonging to complex I or NADH dehydrogenase (ND1, ND2, ND3, ND4, ND4L, ND5, ND6), 1 to complex III or cytochrome c reductase, 3 to complex IV or cytochrome c oxidase (COX I, COX II and COX III), and 2 to complex V or ATP synthase (ATPase6 and ATPase8). These subunits are assembled together with nuclear-encoded subunits. The remaining mitochondrial proteins, including all the complex II subunits, are encoded by nuclear DNA. One mitochondrion can contain two to ten copies of mtDNA. Mitochondrial genetics differs from Mendelian genetics in three major aspects: maternal inheritance, heteroplasmy, and mitotic segregation. Mitochondria are inherited in humans via the female line [3, 5], transmitted as a nonrecombining unit by maternal inheritance [6]. Furthermore, human mtDNA is characterized by a much greater evolutionary rate

than that of the average of nuclear genes. Thus, its sequence variation has been generated by the sequential accumulation of new mutations along radiating maternal lineages. Therefore, mtDNA contains a "molecular record" of the human migrations. We can theoretically follow the transmission of mtDNA from the original "ancestor mother", the "mitochondrial Eve" [7], by identifying common polymorphisms that have been accumulated with time. These common polymorphisms describe classes of continent-specific genotypes, the haplogroups, evolved from the same ancestor, which can be detected by restriction fragment length polymorphism (RFLP) analysis. "Mitochondrial Eve" probably lived in Africa about 200,000 years ago and phylogeographic studies allowed to identify the mtDNA haplogroups tree and the mtDNA migration route (see Figure 1). Because the process of molecular differentiation is relatively fast and occurred mainly during and after the recent process of dispersal into different parts of the world, haplogroups usually tend to be restricted to particular geographic areas and populations.

The basal branching structure of mtDNA variation in most parts of the world is now well understood [6]. The major branches of the tree were usually restricted geographically, some to sub-Saharan Africans, others to East Asians and yet others to Europeans and Near Easterners [8]. African haplogroups fall into seven major families (L0, L1, L2, L3, L4, L5, L6). About 85000 years ago, probably in the Horn of Africa, changes in climate, the glacial interstadial phase 21, triggered the rising of many descendant haplogroups from the root of haplogroup L3, the first multifurcation node, probably because of some colonization event or local population growth [6, 9, 10]. Non-African mtDNA (excluding migrations from Africa within the past few thousand years) descend from L3 and belong either to the M or N superclades. Haplogroup N soon gave rise to haplogroup R. In the Indian subcontinent and in Southeast Asia there is the richest basal variation in the three founder haplogroups M, N, and R, and this suggests a rapid colonization along the southern coast of Asia, about 60000 years ago [6]. 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. The expansions northwards occurred later, about 45000 years ago when technology and climatic conditions enabled the exploration of the interior of Eurasia. One of the more marginal extensions eventually led to the peopling of Europe [6].

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 45000 years ago [6]. European mtDNA variation is surprisingly impoverished in the number of independent basal lineages, compared with the South Asian mtDNA variation, maybe for the peripheral role that the pioneer migration into the Near East and subsequently Europe must have had in the broader "Out-of-Africa" scenario. Complete mtDNA sequencing and the increasing number of samples analyzed allowed subdividing haplogroups in smaller groups identifying younger branches on the mtDNA

evolution tree. Therefore, subhaplogroups classification is continuously evolving [6].

2. Mitochondrial Haplogroups and Medicine

It has been supposed that genetic polymorphisms within the mitochondrial genome might lead to impaired energy generation and to increased amount of ROS, causing subtle differences in the encoded proteins and, thus, minimum changes in mitochondrial respiratory chain OXPHOS activity and free radical overproduction. Increased production of ROS damages cell membranes and further accelerates the high mutation rate of mtDNA. The mtDNA is particularly susceptible to oxidative damage. Because of its vicinity with ROS source (ETC) and because it is not protected by histones and it is inefficiently repaired, mtDNA shows a high mutation rate. Accumulation of mtDNA mutations enhances normal ageing, leads to oxidative damage, and causes energy failure and increased production of ROS, in a vicious cycle. This could predispose to diseases or modify longevity in individual or in a population sharing the same mtDNA genotype. Maybe the opposite could be also true for different polymorphism(s), which could be protective.

Several studies correlate mitochondrial haplogroups with disease's susceptibility or confer them protective roles. In a study of 2008, conducted on 114 healthy Spanish males, Marcuello et al. [11] found that haplogroups J presents with lower VO(2max) (oxygen consumption) than non J variants. J has been related with a lower efficiency of ETC, diminished ATP, and ROS production. Furthermore, the lower ROS production associated to J could also account for the accrual of this variant in elderly people consequent to a decreased oxidative damage [11]. The H haplogroup seemed to be responsible for the difference between J and non-J, and this group also had significantly higher mitochondrial oxidative damage than the J haplogroup, suggesting that ROS production is responsible for the higher VO(2max) found in this variant [12]. In agreement with these results, VO(2max) and mitochondrial oxidative damage were positively correlated. Supporting the hypothesis that J haplogroup may impair the OXPHOS coupling, Pierron et al. [13] demonstrated that J haplogroup was markedly underrepresented among the A3243G mutation carriers. This mutation on the tRNALeu gene (UUR) is one of the most common mtDNA mutation. The phenotypic expression of this mutation is quite variable, ranging from mild to severe clinical phenotypes (MELAS). The authors, in order to explain the epidemiology of haplogroup J and A3243G mutation speculated that this association is lifethreatening, and therefore lethal to the embryo or germ line [13].

One of the most common manifestation of some mitochondrial disease is the presence of retinal pigmentary changes, which are similar to those observed in age-related maculopathy (ARM). Jones et al. [14] demonstrated an association between haplogroup H and a reduced prevalence of this disease, after adjusting for known ARM risk factors.

Haplogroup H1 may be protective for ischemic stroke; in fact, it was found to be significantly less frequent in stroke patients than in controls, when comparing each clade against
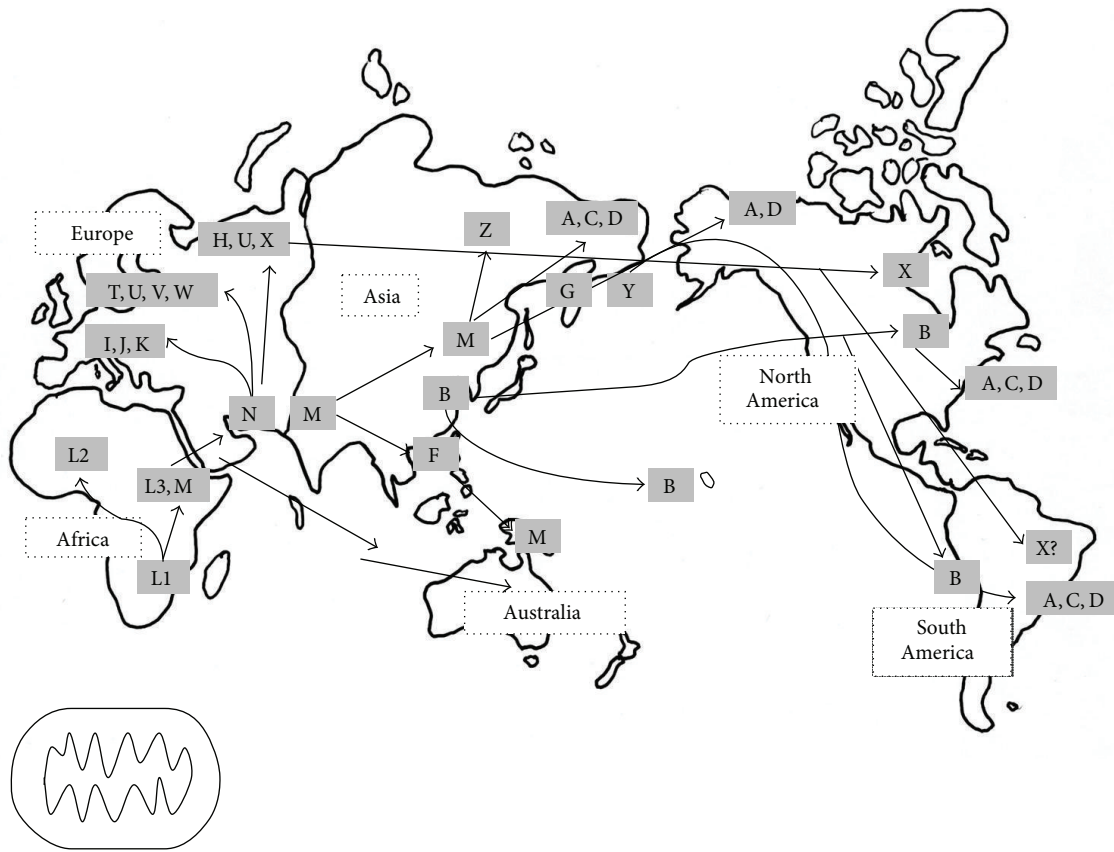
FIGURE 1: MtDNA haplogroup migration patterns. The map shows the migration patterns of the main mtDNA haplogroups.

all other haplogroups pooled together, in a paper of Rosa et al. [15] focusing on 534 ischemic stroke patients and 499 controls.

In a prospective study of intensive care patients in Newcastle-upon-Tyne conducted by Baudouin et al. [16], haplogroup H seemed to confer an increased chance of long-term survival after sepsis than non-H haplogroups (primarily the closely-related haplogroups J and T) maybe for the linkage between mitochondrial dysfunctions and sepsis-induced multiple organ failure demonstrated by Protti and Singer [17]. Two possibilities have been proposed: haplogroup H might protect through greater heat genera- tion (because of higher electron transport rates or looser coupling) [16], or through greater ROS production (because of tighter coupling and raised protonmotive force), which could reduce bacterial infection [18, 19]. Haplogroup R also was a strong independent predictor for survival advantage in severe sepsis with an important impact on long-term clinical outcome [20]. Haplogroup H has been associated with high spermatozoa motility, haplogroup T, instead, with asthenozoospermia, showing significant differences in their OXPHOS performance [21]. However Pereira et al. [22] did not confirm these findings demonstrating no systematic differences between haplotypes from asthenozoospermic samples and those from population surveys. Haplogroup T could be related, instead, with a lower capacity to respond

to endurance training, appearing as a marker negatively associated with the status of elite athletic endurance [23].

Within the Western European, haplogroup J, was asso- ciated with 80% decrease in the risk of progression to neuroretinal disorder [24]. Haplogroups U and K were independently associated with a higher prevalence of age- related hearing loss as described by Manwaring et al. [25] on 912 patients of the Blue Mountains Eye Study cohort. mtDNA haplogroup U, in mitochondrial patients carrying mtDNA single macrodeletion, is associated with a higher relative risk of developing pigmentary retinal degeneration, short stature, dysphasia-dysarthria and cardiac conduction defects, modulating the clinical expression of mitochondrial encephalomyopathies due to mtDNA macrodeletions [26]. mitochondrial dysfunctions have long been hypothesized to be involved in tumorigenesis. Supporting such idea, changes in the number, shape, and function of mitochondria but also mutations in both the noncoding and coding regions of the mtDNA have been reported in various types of cancers [27–29]. In a recent study conducted in China, Fang et al. [30] found that macrohaplogroup M and its subhaplogroup D5 had an increased frequency in breast cancer patients relative to controls but haplogroup M was decreased in the metastatic group; macrohaplogroup N are more likely to exhibit metastatic tumors. Haplogroup D4a was associated with an increased risk of thyroid cancer, while

TABLE 1: A complete list of published researches focusing on mtDNA haplogroups and neurodegenerative diseases.

	Reference	Number of patients	Number of controls	Haplogroups that increase risk	Haplogroups that reduce risk	Sample's region of origin
	Van der Walt et al. [40]	609	340	None	J in females, K in individuals older than 70 years	Europe
	Autere et al. [42]	238	183	supercluster JTIWX increase risk both in Parkinson disease and in Parkinson with dementia	None	Finland
Parkinson's disease	Pyle et al. [41]	455	447	None	cluster UKJT	United Kingdom
	Ghezzi et al. [43]	620	1486	None	K	Italy
	Latsoudis et al. [44]	224	383	None	trend for haplogroups J, T, U and I and the supercluster of haplogroups UKJT to be slightly underrepresented in PD patients	Crete
	Takasaki, [79]	96	96	M7b2, B4e, and B5b	None	Japan
	Simon et al. [45]	168 families	895	None	None	USA (non Hispanic Caucasian)
Amyotrophic lateral sclerosis	Mancuso et al. [46]	222	151	None	I	Italy
	Chinnery et al. [47]	504	493	None	None	United Kingdom
Friedreich's ataxia	Giacchetti et al. [48]	99	48	None	No. However, patients with haplogroup U have a delay of 5 years in the disease onset and a lower rate of cardiomyopathy	Italy
Huntington's disease	Mancuso et al. [49]	51	181	None	None	Italy
	Arning et al. [50]	404	48	haplogroup H associated with a lower age of onset	None	Germany
Multiple sclerosis	Kalman et al. [51]	77	84	K and J	None	Caucasian
	Otaegui et al. [52]	unknown	unknown	unknown	trend for haplogroups JT to be slightly underrepresented in PD patients with multiple sclerosis and multiple sclerosis with optic neuritis	Basque country
	Yu et al. [53]	>2500	>2500	J, 13708A variant	None	Europe (Norway, Spain, Germany, Sardinia, Finland)
	Ban et al. [54]	994	1506	trend for haplogroup U to be overrepresented in patients with multiple sclerosis	None	United Kingdom
	Ghabaee et al. [55]	52	None	Haplogroup A associated with lower age of onset and haplogroup H associated with optic nerve involvement	None	Iran

TABLE 1: Continued.

	Reference	Number of patients	Number of controls	Haplogroups that increase risk	Haplogroups that reduce risk	Sample's region of origin
	Chagnon et al. [74]	69	83	J	T	Quebec, Canada
	Carrieri et al. [77]	213	179 age-matched and 210 individuals aged more than 100 years	None	K and U seem to neutralize the risk effect of the APOE ε4 allele	Italy
	Van der Walt et al. [75]	989	328	U in males	U in females	Europe
	Pyle et al. [41]	185	447	None	None	United Kingdom
Alzheimer's disease	Elson et al. [78]	145	128	None	None	United Kingdom and United States (European descent)
	Mancuso et al. [56]	209	191	None	None	Italy
	Fesahat et al. [76]	30	100	H and U	None	Iran
	Takasaki, [79]	96	96	G2a, B4c1 and N9b1	None	Japan
	Maruszak et al. [80]	222	252	HV	None	Poland
	Tanaka et al. [84]	153	129	np956-965 poly-c insertion and 856A>G variant	None	Japan
	Santoro et al. [81]	936	776	H5, especially in subjects younger than 75 years old	None	Italy

no significant correlation has been detected between any mtDNA haplogroups and colorectal cancer. These evidences suggest that mitochondrial haplogroups may have a tissue-specific, but also population-specific and stage-specific role in modulating cancer development [30].

3. Haplogroups and Aging

In 1992, Harman [31] first proposed the "mitochondrial-free-radical hypothesis", a mitochondrial theory of aging, supposing that accumulation of damage to mitochondria and mtDNA leads to aging of humans and animals and affects longevity. The observation that mitochondrial function declines and mtDNA mutation increases in tissue cells in an age-dependent manner supported his theory. Age-related impairment in the respiratory enzymes not only decreases ATP synthesis but also enhances production of ROS through increased electron leakage in the respiratory chain [31]. The association between longevity and mtDNA haplogroups has been long reported [32–34]. This association is probably population-specific, being evident in centenarians from northern Italy (haplogroup J increase the individual chance to attain longevity) but not in those from southern Italy [34]. In nonagenarians/centenarians from Ireland, Finland, and Japan, mtDNA haplogroups and longevity are also associated. In a recent investigation on longevity in a Japanese population, haplogroup D4b2b, D4a, and D5 have been found associated with centenarians (over 100 years-of-age) and haplogroup D4a with semisupercentenarians (over 105 years-of-age) [35], while another variant (mt9055A,

haplogroup UK) was found to be significantly more frequent in French centenarians [36]. A higher frequency of the J haplogroup and a significantly high frequency of three mtDNA polymorphisms (150T, 489C, 10398G) have also been reported in Finnish long-lived subjects [37]. Castri and colleagues [38] found that the 5178A mutation in haplogroup D is associated with decreased longevity, whereas the 150T mutation is associated with increased longevity in 152 subjects from Costa Rica [38].

4. Haplogroups and Neurodegeneration

Oxidative "free radical" damage is therefore involved in normal aging, but it is also generally viewed as an etiological cause of tissue degeneration, and ROS damage has been reported within specific brain regions in many neurodegenerative conditions [39]. Basing on the evidence that mtDNA variations lead to different OXPHOS performance, than to different oxidative stress profile, the association between haplogroups and neurodegenerative disorders has been long investigated (see Table 1). Van der Walt et al. [40] observed that haplotypes J and K reduced the incidence of Parkinson's disease (PD) by 50%. A further analysis revealed that the SNP at 9055A of *ATP6* (which defines haplogroup K) reduced the risk in women, and the SNP at 13708A of *ND5* gene was protective in individuals older than 70 years (haplogroup J) [40]. The cluster UKJT was associated with a 22% reduction in risk for PD but not with risk of Alzheimer's disease (AD), confirming that the association with PD was disease-specific and not a general effect seen in

all neurodegenerative diseases [41]. The supercluster JTIWX, indeed, increased the risk of both PD and PD with dementia. This cluster was associated with a twofold increase in nonsynonymous substitutions in the mtDNA genes encoding complex I subunits [42]. In a large cohort of 620 Italian PD patients, haplogroup K was associated with a lower risk for PD [43]. In contrast to these evidences, Latsoudis et al. [44] did not observe mtDNA haplogroups that predisposed to PD in 224 PD patients and 383 controls from Crete. A recent study of 2010 [45] conducted on 168 multiplex PD families in which the proband and one parent were diagnosed with PD and 895 controls, in order to investigate the potential contribution of mtDNA variants or mutations to the risk of PD, found no significant differences in the frequencies of mitochondrial haplogroups or of the 10398G complex I gene polymorphism in PD patients compared to controls, and no significant associations with age of onset of PD. Mitochondrial haplogroup and 10398G polymorphism frequencies were similar in probands having an affected father as compared to probands having an affected mother.

To investigate if specific genetic polymorphisms within the mtDNA could act as susceptibility factors and contribute to the clinical expression of sporadic amyotrophic lateral sclerosis (ALS), our group genotyped predefined European mtDNA haplogroups in 222 patients of clear Italian origin with sporadic ALS and 151 matched controls [46]. Mutations on the entire *SOD1* gene were excluded. The frequency of haplogroups I resulted lower in ALS cases than in controls. Age of onset, severity, and neurological system involved in the disease did not associate with haplogroups. In a comparison developed to test what makes this haplogroup I different from the other haplogroups tested, we found highly significant difference in 16391A and 10034C alleles. In accordance with the described study, mtDNA polymorphisms might contribute to motor neuron degeneration, possibly interacting with unknown genetic or environmental factors [46]. However, this finding was not confirmed by Chinnery et al. [47], who studied large UK cohort of 504 ALS patients and 493 controls and found no evidence that mtDNA haplogroups contribute to the risk of developing ALS.

As far as regard Friedreich's ataxia (FA), Giacchetti et al. [48] studied 99 FA patients and 48 control individuals, all from southern Italy revealing that patients with haplogroup U class had a delay of 5 years in the disease onset and a lower rate of cardiomyopathy. However, no significant difference was found in the frequency distribution of haplogroups between patients and controls [48].

Huntington's disease (HD), as FA, is a trinucleotide expansion disorder, caused by a CAG expansion in the IT15 gene. On the basis of the Giacchetti's report [48], we wanted to determine whether mtDNA polymorphisms play the role of "modifier genes" in HD. In this work, we have genotyped 51 patients with HD and 181 matched controls. Only HD subjects with a similar number of triplets (49.3 ± 5.3, range 45–60) were enrolled. The frequency of the haplogroups and haplogroup clusters did not differ between the two groups, and we did not observe correlation with gender, age of onset, and disease status. Over the last 3 years, patients have

undergone prospective evaluations, with a control every 6 months. Different functional scales have been performed. No significant difference was observed between different haplogroups and haplogroup clusters in the cognitive or motor progression of the disease. Therefore, our study did not support the association between mtDNA haplogroup(s) and HD [49]. However, in a recent study, Arning and colleagues [50] demonstrate a significantly lower age at onset in patients carrying the most common haplogroup H [50].

Several lines of evidence suggest that mitochondrial genetic factors may influence susceptibility to multiple sclerosis (MS). Large scale screening of the mtDNA revealed no pathogenic mutations but an association between haplogroups K and J with MS in Caucasians [51]. Another study reported that none of the haplogroups were associated with the disease. There seemed to be a protective trend in the "JT + the protective allele of UCP2" combination [52]. More recently, Yu and colleagues [53] observed that the frequency of haplogroup J was higher in patients than in controls. 13708A variant itself seemed to explain this association and might represent a susceptibility allele for MS [53]. In the same year a study of Ban et al. [54] performed in order to explore this hypothesis further, resequenced the mitochondrial genome from 159 patients with MS and completed a haplogroup analysis including a further 835 patients and 1,506 controls. Haplogroup analysis identified a trend towards an overrepresentation of superhaplogroup U. In addition they also found modest evidence of an association with variations in the nuclear gene NDUFS2 [54]. In 2009, Ghabaee and coauthors studied mtDNA haplogroups, age, gender, clinical disability, course of the disease, and presenting symptoms of 52 MS patients. The prevalent mutations were J, L, and T haplogroups. Haplotype A was more prevalent in patients with younger age of onset and high proportion of haplogroup H was associated with optic nerve involvement. No motor symptoms were seen in haplogroup H patients [55].

5. Haplogroups and Alzheimer's Disease

AD is a brain neurodegenerative disorder named for German physician Alois Alzheimer, who first described it at a scientific meeting in November 1906, presenting the case of "Frau Auguste D." a 51-year-old woman brought to see him in 1901 by her family. Approximately 2-3% of AD cases are early onset and familial, with autosomal dominant inheritance. Mutations in three genes are known to cause familial AD: mutations in the gene of amyloid precursor protein (APP), which is leaved sequentially by b- and c-secretases, and mutations in genes of presenilins 1 and 2 (PS1 and PS2), one or other of which is a component of each c-secretases complex. Although these specific mutations have been associated with the relatively rare forms of familial AD, the causes of the much more frequently occurring sporadic AD remain unknown, and the mechanisms leading to neuronal death are still unclear [56]. Most forms of sporadic late-onset AD have probably a complex aetiology due to environmental and genetic factors, which taken alone, are not sufficient to develop the disease. Presently, age is

the major risk factor for sporadic AD, while the genetic major risk factor is recognized in the presence of allele $\varepsilon 4$ of apolipoprotein E (ApoE4) [57]. However, in the majority of late-onset AD patients, the casual factors are still unknown and genetics factor probably interact with environmental factors or with other pathologic or physiologic conditions to exert the pathogenic effect, such as chronic inflammation [58], excitotoxicity damage [59], oxidative stress [60], and diminished brain metabolism [61]. To date, the "amyloid-β cascade" hypothesis, first proposed in 1992 [62], remains the main pathogenetic model of AD. However, although this cascade is potentially viable in familial AD cases with mutation in APP and PS genes, its role in the sporadic AD is unclear [63].

Although the pathogenic mechanisms of neurodegeneration in AD are not clarified, in the past 15 years, numerous studies have been performed in order to better understand the possible involvement of mitochondria, accumulating evidences suggesting that mitochondrial dysfunction and oxidative stress occur in brain and peripheral tissues of AD patients and supporting the idea that mitochondria may trigger the abnormal onset of neuronal degeneration and death in AD [56].

In order to study the importance and potential causes of mitochondrial dysfunction, the cytoplasmic hybrid ("cybrid") technique, a technique in which mitochondria/mtDNA from human AD and control platelets is transferred to culturable cells depleted of endogenous mtDNA [64], has been applied. The resulting AD cybrids showed a transferred COX defect and revealed a number of consequences that recapitulate the pathology observed in AD brain [65–67]. Remarkably, AD cybrid lines had increased intracellular amyloid accumulation and increased amyloid secretion [65], as well as an increased proportion of morphologically abnormal mitochondria [68]. Trimmer et al. [67] observed that AD cybrid lines show a bioenergetic defect that becomes more severe with passage in culture. AD cybrids also showed elevated spontaneous death with apoptotic nuclear morphology [69], increased cytoplasmic cytochrome c levels and caspase-3 activity [65], and elevated cleavage of caspase substrate [69] not observed in non-AD cybrids. Again, the spontaneous alterations in cell death and cell-death pathways observed spontaneously in AD cybrids can be reproduced by exposing non-AD cybrids to exogenous aggregated beta amyloid or oxidative stress [69, 70]. Despite these reports, a number of technical issues have confounded cybrid studies [71, 72]. However, these studies on cybrid models reinforce the concept that primary mtDNA changes could be responsible for the "mitochondrial features" of sporadic AD and could be the origin of the increased oxidative stress and Aβ deposition found in sporadic AD brain.

With the aim of better clarifing the involvement of mitochondria in the pathogenesis of AD, it has studied the possible association of mitochondrial haplogroups and AD susceptibility. As already discussed, inherited European mitochondrial haplogroups may be related to longevity [37, 73], as well as to neurodegeneration, AD risk, and, thus, death in Caucasians. In a paper of Chagnon et al. [74],

haplogroup T is described underrepresented in AD, while haplogroup J overrepresented [74]. Van der Walt et al. [75] showed that males classified as haplogroup U had a significant increase in risk of AD, while females demonstrated a significant decrease in risk with the same U haplogroup. To assess the relationship between mtDNA haplogroup and AD in an Iranian population, Fesahat sequenced the two mtDNA hypervariable segments in 30 AD patients and 100 control subjects. They found that haplogroups H and U are significantly more abundant in AD patients, assuming that these two haplogroups might act synergistically to increase the penetrance of AD disease [76]. By studying an Italian sample of subjects, Carrieri et al. [77] hypothesized that K and U haplogroups may act by neutralizing the effect of the major AD risk factor ApoE $\varepsilon 4$ allele. However, this association was not confirmed recently by a collaborative study performed by Elson et al. [78], in which the authors analyzed the complete mtDNA coding region sequences from more than 270 AD patients and normal controls. The authors described no statistically significant association between haplogroup and disease status. They also observed that for both synonymous and nonsilent changes, the overall numbers of nucleotide substitutions were the same for the AD and control sequences.

Regarding our experience, in our laboratory we did not find any evidence for an etiological role of haplogroups in AD risk [56]. We studied the frequency of the 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). The frequency of haplogroups was not significantly different between the two groups. Furthermore, there was no significant difference between genders as far as mtDNA haplogroups distribution in both AD patients and control groups is concerned. Takasaki, studying a Japanese population of 96 AD patients, described an association between AD and the haplogroups G2a, B4c1, and N9b1. In addition, to compare mitochondrial haplogroups of the AD patients with those of other classes of Japanese people, the relationships between four classes of Japanese people (96 Japanese centenarians, 96 Parkinson's disease (PD) patients, 96 type 2 diabetic (T2D) patients, and 96 nonobese young males) and their haplogroups are also described. The four classes of people are associated with a set of haplogroups, therefore different from those of the AD Japanese patients [79]. A study conducted on a Polish population found that HV cluster is significantly associated with the risk of AD, regardless of the APOE4 status, reporting no evidence for the involvement of haplogroup U, K, J, or T in AD risk [80].

The most recent report about a possible link between AD and mtDNA genotypes shows evidence for subhaplogroup H5 as a risk factor for late onset AD [81]. Santoro et al. analyzed 936 AD patients and 776 controls comparable for age and ethnicity from the central-northern regions of Italy. Haplogroups H3, H4, H5, and H6 [82] are associated with an increased production of ROS than those with haplogroup T. Accordingly, it was hypothesized that subjects with haplogroup H could be more prone to oxidative stress

than those with other haplogroups [18], and consequently more susceptible to neurodegenerative diseases. They found that subhaplogroup H5 appears to be associated with a higher risk of AD in both the total sample and the female group. They also found that subhaplogroup H5 interacts with age in modifying AD risk; in fact H5 subjects younger than 75 years old had a higher AD risk than non-H5 subjects. Age is a strong risk factor for AD [83] and the authors hypothesized that age 75 could be considered as a threshold, under which risk factors such as subhaplogroup H5 and APOE could independently exert their major effect on the development of the disease, while over this age, other risk factors, such as ageing itself, would largely prevail. Tanaka and colleagues also agree 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 APOE $\varepsilon 4$ allele. The authors however indicate that the np956-965 poly-c insertion and 856A>G variant might be a risk factor for AD [84].

6. Conclusions

In the past 15 years, research has been directed at clarifying the involvement of mitochondria and defects in mitochondrial oxidative phosphorylation in several disorders. It has been speculated that mtDNA mutations that accumulate with age might lead to impaired energy generation and to increased amount of ROS, both resulting in cell damage. Polymorphisms in mtDNA may cause subtle differences in mitochondrial respiratory chain activity and free radical overproduction. This could predispose an individual, or a population sharing the same mtDNA genotype, to an earlier onset of apoptotic processes, such as accumulation of somatic mtDNA mutations and mitochondrial impairment. The opposite could be true for different polymorphism(s), which could be beneficial increasing mitochondrial respiration and/or reducing ROS production [57, 85]. A critical role for mitochondrial dysfunction and oxidative damage in neurodegenerative diseases has been greatly strengthened by recent findings. However, despite the morphological and biochemical evidence of mitochondrial dysfunctions in various tissues of patients with neurodegenerative disorders, the role of the mitochondrial genome and of its haplogroups as a risk factor is still debated. MtDNA haplogroups have been associated with a number of different neurodegenerative diseases, but to date, the only disease consistently associated with a different mtDNA haplogroup frequency is PD. Although it has been suggested that inherited haplogroups K and U may influence AD risk in Caucasians, this is still an unresolved question. To date, mtDNA haplogroups do not seem to play a major role in AD. The mtDNA alterations that cybrid models induce to hypothesize might be due to somatic factors. APP, Aβ-induced mitochondrial toxicity, oxidative stress, somatic mtDNA damage, mitochondrial dysfunction and apoptosis seem to be interconnected in vicious manner that reinforces this dysfunction by causing mtDNA damage, impairment of the mitochondrial respiration and oxidative stress leading to neurodegeneration and dementia. Researches performed in order to allow the identification of AD risk factor also in preclinical stages might be useful in the development of more effective therapeutic interventions at a potentially reversible stage.

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