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# Mitochondrial DNA in pathogenesis of Alzheimer's and Parkinson's diseases

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Review

**Abstract.** A critical role of mitochondrial dysfunction and oxidative damage has been implicated in etiopathology of many neurodegenerative disorders, as well as in normal aging. Alzheimer's and Parkinson's diseases are common devastating late-onset neurodegenerative disorders, associated with mitochondrial DNA variations, which are suggested to affect mitochondrial functions. This paper reviews the current knowledge on the inherited and somatic mtDNA variations in both conditions.

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**Key words:** mitochondrial DNA, Alzheimer's disease, Parkinson's disease, haplogroups, single nucleotide polymorphisms, neurodegeneration

## CONTENTS



## INTRODUCTION

A wide spectrum of diseases has been associated with mitochondrial DNA (mtDNA) variations. The typical inherited mtDNA disorders, such as mitochondrial encephalomiopathy, lactic acidosis and stroke-like syndrome (MELAS), miotonic epilepsy, and ragged red fiber disease (MERRF) or Leber's hereditary optic neuropathy (LHON), encompass very characteristic syndrome subsets and are characterized by phenotypic manifestation mainly in infancy or early adulthood. Apart from diseases with clear mitochondrial basis, mitochondrial dysfunctions have been associated with aging and age-related neurodegenerative diseases, such as Alzheimer's disease (AD) and Parkinson's disease (PD). Here we review the current state of knowledge concerning the latter diseases.

Alzheimer's and Parkinson's diseases are common devastating neurodegenerative disorders, affecting millions of the elderly worldwide. Although they constitute distinct disease entities, they share some features. AD individuals may exhibit parkinsonian symptoms and concurrent neuropathological features of PD, including substantia nigra degeneration and Lewy bodies in the pigmented nuclei and nuclei basali (Garcia-Lozano et al. 2002, Hulette et al. 1995). Similarly, PD patients present frequently dementia that may be associated with AD morphopathology (Garcia-Lozano et al. 2002, Hulette et al. 1995). The overlapping phenotypic features of AD and PD implicate related etiological mechanisms (Egensperger et al. 1997, Garcia-Lozano et al. 2002).

Epidemiological data indicates that the risk of developing AD and PD is greater for a person whose mother was affected by the disease in comparison with an offspring of an affected father (Beal 1998, Bonilla et al. 1999, Chinnery et al. 1999). To date, there is no satisfactory explanation for the hypothetical maternal effect. However, it is accepted that inherited and somatic mtDNA variations can contribute to the etiology of both disorders.

Human mtDNA is highly polymorphic and more vulnerable to mutations than nuclear DNA (nDNA). The frequency of single nucleotide polymorphisms (SNPs) in mtDNA was estimated as 1 SNP per every 13 bp, so it is 70 times higher than that of nuclear SNPs (Tanaka et al. 2004). Similarly, somatic mutations are accumulated in mtDNA 17 times faster than in nDNA (Cantuti-Castelvetri et al. 2005, Reddy and Beal 2005). There are some factors implicated in promoting the higher rate of mitochondrial mutations. First, mtDNA is exposed to much stronger oxidative stress, as it is situated in the proximity of the electron transport chain (ETC), the major source of intracellular reactive oxygen species (ROS). Second, mitochondrial genome is not protected by histones and any damage to mtDNA can be repaired through base but not nucleotide excision repair (Reddy and Beal 2005, Sawyer and Van Houten 1999). Moreover, mtDNA is replicated more frequently than nDNA, thus mutations are likely to result from replication copy errors that can be unprovoked, promoted by DNA damage or imbalance in mitochondrial dNTP pools (Kaguni 2004, Kang and Hamasaki 2005, Song et al. 2005). Particularly rich in mutational hotspots is the control region (CR), the fragment of mitochondrial genome lacking any known coding DNA (Tanaka et al. 2004).

MtDNA somatic mutations are believed to propagate by "clonal expansion" i.e., accumulation of the progeny of the single initial mutated DNA molecule (Clarke 2000, Coskun et al. 2004, Nekhaeva et al. 2002, Yoneda et al. 1992 ). This could be an effect of stochastic redistribution of mitochondria carrying mutated mtDNA molecules during cell division or, alternatively, result from a particular advantage offered by a mutation, such as faster replication of shorter mtDNA copies (Clarke 2000, Lee and Wei 2000).

According to the threshold burden concept, a mutated mtDNA can affect cell physiology only if it has accumulated to a significant level. The threshold value depends on the tissue type, mutation nature and is influenced by age and environmental factors (Berdanier and Everts 2001, Chinnery and Schon 2003, Clarke 2000). The phenotypic expression of mtDNA can vary due to the interplay between inherited mutations and accumulated somatic ones. It could also be affected by the shifts in the percentage of the mutated mtDNA in single cells, ascribed to mtDNA amplification independent of the cell cycle ("relaxed replication") and mtDNA mitotic segregation in dividing cells (Chinnery and Schon 2003).

Graduate accumulation of low levels of potentially pathogenic mutations in somatic cells has been proposed to accompany aging. Particularly, this is a postulate of the mitochondrial theory of aging, a variant of the free radical theory of aging (Harman 1972, Linnane et al. 1989). Evidence in favor of this theory comes from the recent findings of Smigrodzki and Khan (2005) who revealed that in aged adults the vast majority (>90%) of mtDNA is mutated. They demonstrated that in the aged individuals the abundance of a particular mutation is low (1–2%), making it undetectable with conventional mutation detection techniques (Smigrodzki and Khan 2005). Low-level heteroplasmy (microheteroplasmy) observed by Smigrodzki and Khan, is characterized by the presence of multiple rare mutations, including inherited mutations, *de novo* germline mutations and somatic mutations in one organism. Since it appears unlikely that any single mutation in an individual would reach a high enough level to become responsible for mitochondrial decline (Byrne 2002, Lin et al. 2002), it has been proposed that the aggregate burden of random mutations might determine the rate of individual's aging, as well as could be critical for the pathomechanism of age-associated diseases, such as AD and PD (Cantuti-Castelvetri et al. 2005, Lin et al. 2002, Smigrodzki and Khan 2005). However, the phenotypic threshold of microheteroplasmy remains unclear (Smigrodzki and Khan 2005). Although a variety of individual point mutations have been observed to increase with age, they have not been consistently reproduced or confirmed by others and no single aging-specific mutation has been identified (Lin et al. 2002).

Although mtDNA codes for only 2% of all proteins forming the subunits of the mitochondrial respiratory chain (Table I), all of them are essential for maintaining physiological oxidative phosphorylation (OXPHOS). Consequently, the increasing number of mtDNA mutations has been proposed to be causally related with the decline of the energetical capacity of the cell in an aging organism (Cantuti-Castelvetri et al. 2005, De Benedictis et al. 1999).

The most likely culprit of mitochondrial genome abnormalities is the activity of free radicals or ROS, for which the largest cellular source (90%), and the target at the same time, are mitochondria (Berdanier and Everts 2001, Enns 2003, Kang and Hamasaki 2005, Melov 2004). ROS are physiologically significant by-products of cellular aerobic metabolism, however they are potentially toxic [reviewed by Melov (2004)]. Recently, a study showing lifespan extension in trans-

Table I

The role of mitochondrial genome in encoding respiratory chain subunits

| Complex | Enzyme | Number of all subunits in a complex | mtDNA encoded subunits |
|---|---|---|---|
| I | NADH ubiquinone reductase | 43 | 7 (ND1, 2, 3, 4, 4L, 5, 6) |
| II | Succinate ubiquinone reductase | 4 | – |
| III | Ubiquinol cytochrome c reductase | 11 | 1 (cytochrome b) |
| IV | Cytochrome c oxidase (COX) | 13 | 3 (COX1, COX2, COX3) |
| V | ATP synthase | 17 | 2 (ATPase 6, ATPase 8) |

genic mice overexpressing human catalase in mitochondria has lent support to the proposed involvement of ROS in aging (Schriner et al. 2005). Interestingly, in comparison with the littermate controls, the genetically engineered mice lived 20% longer without apparent deleterious side-effects (Schriner et al. 2005).

When ROS levels exceed the cellular antioxidant defenses, a deleterious condition known as oxidative stress occurs. Excessive ROS drive the oxidative damage to mitochondrial and cellular nucleic acids, proteins, and lipids and can result in a downregulation of ETC (Reddy and Beal 2005). Inhibition of ETC leads to accumulation of electrons in the early stages of ETC (complex I and coenzyme Q), where they prompt further ROS generation (Reddy 2006).

Mitochondria are pivotal in the initiation of programmed cell death and any damage to mtDNA can indirectly drive apoptosis and, consequently, loss of tissue function (Emerit et al. 2004, Susin et al. 1998, Smigrodzki and Khan 2005). Progressive accumulation of mtDNA mutations and associated mitochondrial impairment are indicated to play a role not only in aging but also in neurodegenerative diseases. Accumulating evidence implies that oxidative stress is one of the earliest and perhaps crucial events in the pathogenesis of AD and PD, for which age is the major risk factor (Egensperger et al. 1997, Howell et al. 2005). It has been suggested that in patients with AD or PD the rate of accumulation of mtDNA mutations in brain tissue is much faster than in healthy individuals (Chinnery et al. 1999). High lipid content, relatively high oxidative metabolism and low level of antioxidant defenses make the brain very susceptible to oxidative stress (Emerit et al. 2004, Moreira et al. 2005, Reddy and Beal 2005). Additionally, neurons are terminally differentiated cells, leaving no chances for replacement of the demised cells. In AD and PD the neural cell death occurs predominantly by apoptosis driven by a series of interactive processes, such as disrupted calcium homeostasis, activation of nitric oxide synthetase, free radicals generation, glutamate related neurotoxicity, and dysfunction of the mitochondrial respiratory chain (Emerit et al. 2004, Friedlander 2003).

It is a matter of debate, if the impairment of mitochondrial function is primary or secondary to the neurodegenerative process in AD and PD (Schapira 2002, Swerdlow and Khan 2004). The hypothesis stating that the mitochondrial abnormalities have a key role in the diseases suggests also the existence of selective defects for both AD and PD (Howell et al. 2005, Schapira 2002). So far, the impairment of OXPHOS has been generally assigned to a decrease in activity of the mitochondrial respiratory chain complex IV in AD and complex I in PD (Anandatheerthavarada et al. 2003, Byrne 2002, Coskun et al. 2004, Egensperger et al. 1997, Kang and Hamasaki 2005). The relevant genetic factors still remain elusive, and apart from somatic mutations, inherited mtDNA variations could also be a causally related factor.

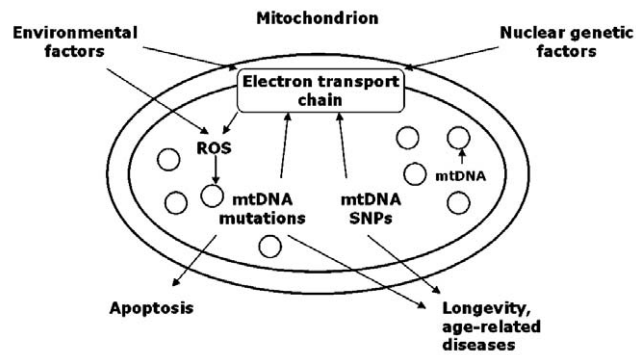


Fig. 1. Schematic representation of the influence of genetic and environmental factors on mitochondrial functions, mtDNA, cell viability, and organism

### mtDNA variation in longevity, normal aging, and neurodegenerative disorders

MtSNPs are classified according to their evolutionary past into sets of substitutions inherited as blocks (haplotypes). Each haplogroup encompasses many haplotypes, consisting of numerous SNPs (De Benedictis et al. 1999). Since mtDNA variation is continent-specific, haplotype analysis enables retracing origins of human species to Africa (Wallace et al. 1999), where the most variable and ancient haplogroups L0, L1, L2, and L3 predominate. These haplogroups formed M and N macrohaplogroups that spread to Euroasia. In the Asians haplogroups A, B, C, D, F, G, and certain subclusters of macrohaplogroups M and N are detected, whereas haplogroups A, B, C, D, and X are characteristic for the native Americans and haplogroups H, I, J, K, T, U, V, W, and X (falling into four clusters: HV, UK, WIX, and TJ) for the Europeans (Herrnstadt et al. 2002, Kong et al. 2003, Finnila et al. 2001, Niemi et al. 2005, Piechota et al. 2004, Silva et al. 2002, Tanaka et al. 2004).

The data from evolutionary and population studies indicate that mtDNA inherited variability (i.e. certain

haplotype or haplogroups) could increase resistance to age-related diseases, such as AD and PD, and to promote longevity (Table II) (De Benedictis et al. 1999, Ivanova et al. 1998, Niemi et al. 2003, 2005, Ross et al. 2001, Tanaka et al. 2000). It has been suggested that certain mtDNA types have been selected on the basis of their protective effect for mitochondrial functions. This in turn could have increased the probability of successful aging and longevity (De Benedictis et al. 1999). De Benedicts and coauthors (1999) remark that longevity is a multifactorial trait, strongly dependent on environmental factors as well as on the entire genetic background, thus each ethnic group may have its own disease- or longevity-related mtSNPs and different gene/longevity associations.

Currently, in the European aged population haplogroup J and four mtSNPs are believed to influence senescence. The association between haplogroup J and longevity was reported in the northern Italians and Finns studies (De Benedictis et al. 1999, Dato et al. 2004, Niemi et al. 2003). Among the Italian centenarians haplogroup J was more frequent among males than in controls and female centenarians, and among the overall centenarian group (23%), compared to younger individuals (2%) (De Benedictis et al. 1999). It has been speculated that haplogroup J might improve starting OXPHOS levels, which in turn could delay age-associated diseases (De Benedictis et al. 1999).

Furthermore, in the same two centenarian populations polymorphism C150T has been reported to be more prevalent (Dato et al. 2004, Niemi et al. 2005, Zhang et al. 2003). Position C150 is a well known mutational hotspot within the mitochondrial CR in many unrelated haplogroups such as H, U, J, and T (Allard et al. 2002). It is located near the origin of heavy (H)-strand replication and has been hypothesized to alter the replication origin (Niemi et al. 2005, Zhang et al. 2003).

Recently, Niemi and others have associated 150T with longevity in subhaplogroups (J2, D5, and M7b) of the European and Asian populations harboring two additional mtSNPs, 10398G and 489C (Niemi et al. 2005). Combination of these alleles is believed to play a greater role in determining longevity than each of the alleles separately (Niemi et al. 2005). Nevertheless, further studies should consider epistatic interactions involving different *loci*. It is also possible that concrete mtSNPs could be only a marker for other linked mitochondrial polymorphisms causally involved in longevity (Ross et al. 2001).

Table II

Review of reported mtSNP characteristic for centenarians in different world populations

| Population | mtSNP | Location, mtDNA haplogroup | The effects of mtSNP | Reference |
|---|---|---|---|---|
| Japanese | C5178A | *ND2*, haplogroup D | Leu>Met substitution conferring resistance to adult-onset diseases by suppressing obesity and artheriosclerosis; decelerates the mitochondrial mutagenesis; longevity-associated | Tanaka et al. 2000, 2004 |
| French, Irish | G9055A | *ATP6*, haplogroup K | Ala>Ser substitution; longevity-associated | Ivanova et al. 1998, Ross et al. 2001 |
| Northern Italian, Finnish | haplogroup J | | longevity-associated | De Benedictis et al. 1999, Dato et al. 2004, Niemi et al. 2003 |
| Finnish | 150T, 10398G and 489C | 150T and 489C in non-coding region, 10398G in *ND3* | epistatic interactions of 150T, 10398G and 489C play a role in determining longevity | Niemi et al. 2005 |

In the French population, another mtSNP, G9055A (characteristic for haplogroup K), located in the ATP synthase 6 (ATP6) gene was statistically more frequent in centenarians (13.7%) than in adult controls (6.6%) (Ivanova et al. 1998). In the Irish aged population 9055A was also found at an increased frequency (9%) compared to the control group (5%), however it failed to reach the level of statistical significance (Ross et al. 2001). Moreover, a protective effect of this mtSNP is also postulated in PD (as discussed below).

Outside Europe longevity seems to be associated with different patterns of mtDNA variability. Tanaka and colleagues (1998, 2000, 2004) identified in the Japanese a longevity-associated mtSNP C5178A (L237M) in the NADH dehydrogenase subunit 2 (ND2) of complex I. The polymorphism characterizes haplogroup D and it is a part of the macrohaplogroup M, very frequent in Asia, whereas practically absent in Europe (De Benedictis et al. 1999, Lorenc et al. 2004, Ross et al. 2001, Tanaka et al. 2000). The frequency of C5178A was significantly higher in the centenarians (62%) than in the healthy control group (45%) (Tanaka et al. 2000). Moreover, the ratio of 5178A to 5178C among 145 patients with various mitochondrial disorders (42:103) was found to be significantly lower than in healthy controls (277:356). It was postulated that the 5178A allele decelerates the accumulation of mtDNA mutations in somatic cells with advancing age (Tanaka et al. 2000).

Based on the findings of the characteristic mtSNPs for European and Japanese centenarians, it has been proposed that there are also mtDNA variations conferring the risk of developing age-related neurodegenerative diseases. Tanaka and coauthors (2004) have speculated that certain mtSNPs predisposing to the diseases with high age of onset, escaped natural selection in the past, when the average lifespan was low.

Notably, there are polymorphisms suspected to influence both AD and PD. Van der Walt and colleagues (2004) reported an association of G10398A with the incidence of both PD and AD. G10398A, which causes a non-conservative amino acid substitution (Ala to Thr) in NADH dehydrogenase subunit 3 (ND3) of complex I, has been postulated to alter its structure and in turn to increase the rate of electron leakage and ROS generation (Canter et al. 2005). Apart from AD and PD the 10398A variant is a putative risk factor predisposing to Friedreich's ataxia, amyotrophic lateral sclerosis, and breast cancer in African-American women (Canter et al. 2005, van der Walt et al. 2003, 2004).

The $tRNA^{Gln}$ mutation, A4336G, is another mtDNA variation associated with AD and PD. The nucleotide 4336 joins the amino acid acceptor stem with the TψC stem of the $tRNA^{Gln}$ and is conserved not only in humans (Egensperger et al. 1997). Since mitochondrial tRNA can function as a signal for RNA processing, it is suspected that 4336G could provoke mitochondrial translation impairment which in turn could result in defects in OXPHOS (Egensperger et al. 1997).

There are contradictory results concerning the A4336G polymorphism. Some studies found 4336G to be significantly more frequent in patients with AD or PD than in age-matched or Caucasian controls (Egensperger et al. 1997, Hutchin and Cortopassi 1995, Otaegui et al. 2004, Shoffner et al. 1993) (see Table III). They support the hypothesis that 4336G is a susceptibility factor for both AD and PD. However, Wragg and coauthors reported a decreased frequency of 4336G in AD patients compared with the control group (Wragg et al. 1995). García-Lozano and colleagues (2002) found that 4336G occurred at a similar frequency among both groups of patients with AD or PD and the control group. In addition, the data obtained by other researchers do not provide evidence for a possible implication of this mtSNP in the pathogenesis of PD (Bandmann et al. 1997, Simon et al. 2000).

Considering the outcome of numerous studies on 4336G, it seems rather unlikely that it would be associated with the incidence of either disease. Nevertheless, it could be speculated that mtDNA carrying 4336G may interact with other nuclear, physiological or environmental factors, leading to an increased risk of developing neurodegenerative disease (Chinnery et al. 1999, Egensperger et al. 1997).

## INVOLVEMENT OF MITOCHONDRIAL DNA VARIATION IN ALZHEIMER'S DISEASE

Alzheimer's disease is the most common neurodegenerative disease, characterized clinically by the cognitive impairment and changes in behavior and personality. AD is associated with two hallmark lesions: senile plaques, assembled from β-amyloid (Aβ) peptides, and neurofibrillary tangles (NFT), consisting mainly of tau protein (Zekanowski et al. 2004).

AD is a multifactorial disease with both genetic and non-genetic causes, and still elusive etiology. Approximately 1–5% of AD cases exhibit an autosomal

Table III

Comparison of A4336G frequencies among AD and PD patients

| Reference | Frequency in AD patients | Frequency in PD patients | Frequency in the control group |
|---|---|---|---|
| Egensperger et al. 1997 | 3.6% (1/28) | 8.7% (2/23) | 0% (0/100), age matched controls |
| Shoffner et al. 1993 | 3.2% (2/62) | 5.3% (2/38) | 0.7% (12/1691) |
| Hutchin and Cortopassi 1995 | 4.1% (8/194) | - | 0.3% (1/322), age matched controls |
| Wragg et al. 1995 | 0.6% (1/155) | - | 3.8% (4/105) |
| García-Lozano et al. 2002 | 0.6% (1/161) | 2.8% (3/106) | 1.3% (1/78) in the age matched controls and 1.4% (2/144) in the randomly chosen controls |
| Bandmann et al. 1997 | - | 2/100 | 2/100 |
| Edland et al. 2002 | (6/236) | - | (7/328), age matched controls |
| Otaegui et al. 2004 | - | 4.9% (5/102) | 0% (0/112), age matched controls |
| Simon et al. 2000 | - | 2.4% (6/252) | 2% (4/200) |

dominant mode of inheritance and in ca. 50% of them mutations in one of the three genes (amyloid precursor protein (*APP*), presenilin 1 (*PSEN1*) or presenilin 2 (*PSEN2*) are found. The remaining majority of AD patients are affected by the sporadic form of the disease (SAD, sporadic AD) which is believed to result from a complex interaction between predisposing genes and other factors, including environmental ones. So far, the only known genetic risk factor for SAD is the *APOE* genotype. Several epidemiological studies have associated *APOE4* allele with an increased risk of developing AD (Styczynska et al. 2003). However, for the majority of patients the causal factors remain undefined.

**Energetic metabolism deficiency in AD**

It is widely accepted that altered AD brain metabolism precede neuropsychological impairment and atrophy, constituting its early and prominent feature (Bonilla et al. 1999, Sullivan and Brown 2005, Swerdlow and Kish 2002). The positron emission tomography (PET) demonstrated reduced cerebral metabolism restricted only to affected brain regions (Reddy and Beal 2005). PET scans show region-specific depressed glucose metabolism and increased oxygen utilization declining with time (Cooper and Schapira 1997, Fukuyama et al. 1994). Postmortem assessment of brain tissue from AD patients has demonstrated defects in mitochondrial enzyme activities, increased oxidative damage and elevated caspase activity (Coskun et al. 2004, Gibson et al. 1998, Sullivan and Brown 2005). In particular, mitochondrial dysfunction in AD has been ascribed to the deficiency in the activity of the terminal electron acceptor in OXPHOS, complex IV and decreased expression of the nuclear and mtDNA encoded subunits of cytochrome c oxidase (Schapira 2002). However, complex IV deficiency, unlike the complex I activity defect in PD, is not AD specific, and it has also been observed in Friedrich's ataxia and spinocerebellar ataxia-1 (Schapira 2002).

**Oxidative stress is intimately associated with AD**

The alterations of oxidative metabolism in AD were noted by Friede in 1965 and since then a plethora of evidence has implied oxidative stress in AD develop-

ment (Friede 1965). Compared to non-demented, age-matched controls AD patients brain tissues were frequently reported to exhibit increased levels of oxidatively altered lipids, proteins and nucleic acids (Behl and Moosmann 2002, Reddy and Beal 2005).

Analogically to the free radical theory of aging and consistently with the collected data, the oxidative-stress hypothesis has been proposed for late-onset SAD pathogenesis (Behl and Moosmann 2002). Although impairment of OXPHOS is regarded as a significant cause of oxidative stress in AD brains, there is still controversy, as to whether oxidative damage precedes and contributes directly to AD pathogenesis. Recent studies highlighted some key issues that should be considered when trying to interpret the defects in mitochondrial metabolism in AD: (i) mtDNA genes sequence variations, (ii) mutations in the control region of mtDNA, (iii) decreased gene transcription, (iv) alterations in mitochondrial enzymes due to oxidative damage and (v) Aβ impact on mitochondrial functions (Rodriguez-Santiago et al. 2001).

According to the amyloid cascade hypothesis, the primary event in AD neurodegeneration is increased production of Aβ peptide, leading to the disease *via* formation of amyloid plaques (Hardy 1997, Selkoe 1998). Experimental support for the role of Aβ in the sequence of events in AD development is predominantly based on studies of the effect of mutations in the *APP, PSEN1* and *PSEN2* genes on elevation of Aβ in brain tissue of patients with familial AD (Hardy 1997, Selkoe 1998). However, the amyloid cascade hypothesis does not provide explanation as to what initiates amyloid plaques formation in the absence of AD mutations. Thus, the application of the hypothesis to SAD has been argued (Kontush 2004, Swerdlow and Khan 2004). Moreover, the amyloid cascade hypothesis has been challenged because in the APP transgenic mice the signs of electrophysiological and behavioral changes appear before plaque formation and the plaque load does not correlate closely with cognitive impairment (Duchen 2004). Additionally, Aβ plays an essential, physiological role in synaptic function, plasticity, learning and memory (Atwood et al. 2003, Kontush 2004, Koudinov and Berezov 2004).

#### Mitochondrial cascade hypothesis for AD

There have been many attempts to elucidate the relationship between Aβ and oxidative stress-related changes, however, an unresolved question persists whether Aβ production is an up- or down-stream process to oxidative damage in SAD patients brains (Behl and Moosmann 2002, Coskun et al. 2004, Giasson et al. 2002, Gu et al. 1998, Smith et al. 2005). Recently, in an attempt to solve this problem, Swerdlow and Khan (2004) have proposed a mitochondrial cascade hypothesis that unifies late-onset SAD histopathology and pathophysiology and posits how SAD might be combined through mitochondrial dysfunction with the amyloid cascade. According to the hypothesis, mitochondrial impairment associated with low rates of OXPHOS increases cell reliance on anaerobic glycolysis and elevated mitochondrial ROS production. The authors claim that mitochondrial malfunction represents a primary pathology in AD, driving both amyloid plaques and NFT formation. It is proposed that the basal ETC efficiency and ROS production are determined by inherited polymorphisms in both mtDNA and nDNA genes of ETC subunits. The level of ROS correlates with the pace of oxidative damage to cellular molecules, including mtDNA. Resulting from the destructive activity of ROS on mtDNA and/or the course of physiological aging, the acquired mitochondrial somatic mutations drive further reduction of ETC activity.

Swerdlow and Khan (2004) indicate that in terminally differentiated neurons the overproduction of ROS yields Aβ generation, which in the initial phase of AD development is currently considered as a compensatory response and primary line of antioxidant defense of the cells. It is in line with the recent findings, showing that Aβ is a bioflocculant binding redox metal ions and preventing them from redox cycling with other ligands (Robinson and Bishop 2002). Metal-chelated Aβ is subsequently secreted from the cytoplasm *via* the Golgi apparatus to the extracellular space and precipitates into insoluble plaques believed to represent an efficient means of presenting toxins to phagocytes. However, at some threshold level of ROS production in the course of AD, the antioxidant activity of Aβ evolves into pro-oxidant. Given the accelerated ROS generation, Aβ is produced in high, non-physiological levels. As a result, an efficient removal of metal-chelated Aβ complexes would be overtaken by the growth of plaques and the vicious circle of increased ROS and Aβ generation would be thus established (Atwood et al. 2003). Moreover, APP has been found to accumulate in the mitochondrial membrane

where under pathological conditions causes perturbation of ETC and increases the level of oxidative stress (Swerdlow and Khan 2004).

Suprathreshold amounts of ROS and/or subthreshold OXPHOS in terminally differentiated neurons elicit apoptosis, removing the most dysfunctional cells. In the still viable cells the impairment of OXPHOS increases the reliance on glycolysis, further altering ROS homeostasis and initiating hypoxic signaling. The latter events constitute a signal for neuronal progenitors to re-entry the cell cycle that eventually fails with the resultant aneuploidy, tau phosphorylation and NFT formation (Swerdlow and Khan 2004).

Swerdlow and Khan (2004) apply the mitochondrial cascade hypothesis exclusively to the case of late-onset SAD, although increased oxidative damage has been observed in both sporadic and familial AD patient brains (Migliore et al. 2005). Nevertheless, the authors posit that in the familial AD oxidative changes are secondary to amyloidogenesis, which in contrast to SAD is strictly a toxic phenomenon.

Mitochondrial cascade hypothesis is one of many suggestions for mitochondrial involvement in the development of late-onset SAD proposed in recent years. Parallel models stipulate the opposite sequence of events, claiming that Aβ is the cause of oxidative stress. They support the possibility that Aβ-mediated neuronal death is associated with an enhanced ROS production and impairment of the ETC activity by inhibiting cytochrome c oxidase, α–ketoglutarate dehydrogenase and puruvate dehydrogenase activities (Behl and Moosmann 2002, Casley et al. 2002, Crouch et al. 2005, Enns 2003, Reddy and Beal 2005, Teng and Tang 2005). These enzymes were reported to be decreased in AD brains, however, only the studies on the defects in cytochrome c oxidase were consistent (Sullivan and Brown 2005).

Recently, dimers of Aβ have been shown to inhibit cytochrome c oxidase (Crouch et al. 2005). The diminished levels of cytochrome c oxidase, a carrier in ETC, are reported to drive increased ROS production (Sullivan and Brown 2005).

Concomitant with these studies, one of the models proposes that the gradual mitochondrial dysfunction does not depend on any genetic variation and is induced by intraneuronal accumulation of insoluble Aβ, and internalization of Aβ in the mitochondrial membrane (Aleardi et al. 2005). Another suggestion for Aβ-related mitochondrial dysfunction derives from Lustbader and colleagues' (2004) demonstration of Aβ-binding alcohol dehydrogenase (ABAD) that accumulate inside mitochondria of AD patients and transgenic mice. Although there are reports that Aβ-ABAD complex perturbs mitochondrial function in AD, leading to leakage of ROS and cell death (Lustbader et al. 2004, Teng and Tang 2005), the Aβ-ABAD interaction needs to be further researched. Moreover, in a transgenic mouse model of AD Anandatheerthavarada and coauthors (2003) showed that APP may be targeted to cortical neuronal mitochondria under certain physiological and pathological conditions. The aggregation of the full length APP in the mitochondrial compartment in membrane arrested form was reported to cause mitochondrial impairment (Anandatheerthavarada et al. 2003). There are other proposed functions of Aβ, however the cumulative evidence still blurs the role of Aβ in AD.

**Primacy of oxidative stress in AD pathogenesis**

All in all, the previous suggestions that mitochondrial dysfunction could only worsen the clinical features of AD (Manfredi and Beal 2000, Rodriguez-Santiago et al. 2001) have been replaced by the notion that mitochondrial abnormalities are critical for the initiation of late-onset SAD (Reddy and Beal 2005). Emerging body of evidence supports the primacy of mitochondrial oxidative stress in AD pathogenesis (Atwood et al. 2003, Migliore et al. 2005, Moreira et al. 2005, Obrenovich et al. 2002, Perry et al. 2000, Robinson and Bishop 2002, Savory et al. 2002, Smith et al. 2005). Current findings expand our knowledge about AD neuropathology by revealing that the NFT formation, although historically regarded as a toxic mediator of AD pathogenesis (Egensperger et al. 1997, Liu et al. 2005, Reddy and Beal 2005), similarly to amyloid plaques, could be also a consequence of oxidative stress and serve as an antioxidant protection (Cash et al. 2002, Lee et al. 2005, Obrenovich et al. 2002, Perry et al. 2000, Smith et al. 2005). Moreover, it has been demonstrated that amyloid plaques and NFT load in the cortex of AD brains is inversely correlated with oxidative stress, thus oxidative damage decreases with the disease progression (Atwood et al. 2003, Migliore et al. 2005).

**Inherited mtDNA variation in AD**

It is widely accepted that genetic factors, acting independently or interacting with other genetic and/or

environmental factors, modify the risk of AD. Several studies indicate that maternally inherited mtDNA point mutations might be involved in the pathogenesis of AD. These findings are in line with observations of higher incidence of AD in mothers compared to fathers of the probands (Beal 1998, Bonilla et al. 1999, Chinnery et al. 1999). Considering maternal transmission, mitochondrial haplogoups have been proposed to influence AD risk. Carrieri and coauthors have suggested that in the Caucasian population haplogroups K and U may modulate the susceptibility to AD by neutralizing the effect of the *APOE4* genotype (Carrieri et al. 2001). However, van der Walt and colleagues do not support the association of haplogroup K with a decreased risk of AD (van der Walt et al. 2004). In contrast to Carrieri and others reports, it was demonstrated that males (but not females) belonging to the haplogroup U and carrying the 10398A allele showed an increased risk of AD compared to males with the G allele (van der Walt et al. 2004).

Conversely, in females polymorphisms 12308G and 7028T were demonstrated to decrease the risk of AD, most likely by contributing to the protective effect of haplogroup U (van der Walt et al. 2004). Although *APOE* has been ascribed allele-specific antioxidant activities parallel to the number of cysteins in the *APOE* (E2>E3>E4) (Cash et al. 2002, Miyata and Smith 1996), van der Walt and coauthors results were *APOE* status independent (van der Walt et al. 2004).

The gender-dependent risk conferred by haplogroup U was revealed also in other studies, reporting haplogroup U less frequent among male centenarians (4%) than among control males (23%) and more frequent in AD males (13.3%), as compared to age-matched controls (6.8%) (De Benedictis et al. 2001, van der Walt et al. 2004). Together, these findings suggest that haplogroup U may have a negative effect on aging in Caucasian males (van der Walt et al. 2004).

#### Somatic mtDNA mutations in AD

Alternatively and coherently with the mitochondrial theory of aging, emerging evidence suggests that AD patients aggregate mtDNA mutations in brain tissues (Coskun et al. 2004, Lin et al. 2002, Reddy and Beal 2005). Postmortem application of the biomarker of nucleic acid damage, 8-hydroxy-2'-deoxyguanosine (8OHdG), demonstrated a three-fold increase of its accumulation in mtDNA in AD tissues, compared to age-matched controls (Beal 1998, Mecocci et al. 1994). Likewise, *in vitro* studies of AD patients mtDNA expression in cell lines have shown a decline in the ETC, attributed to mtDNA mutations (Lin et al. 2002).

Assuming the replicative advantage of mutated mtDNA copies, specific mtDNA variants can prevail in a tissue in accord with the rule that the earlier the mutation occurs, the more cells would inherit this variant (Clarke 2000, Coskun et al. 2003, 2004, Howell et al. 2005). However, if mtDNA mutations are to be involved in AD pathogenesis, this mechanism in neurons would have to appear at a very early stage of development to reach a significant level in the brain tissue of the patients. Howell and others (2005) argue that the chance of it is extremely low.

Lin and coauthors (2002) investigated a 1197-bp cytochrome c oxidase subunit 1 and reported that in this region mtDNA from brains of AD and elderly subjects had a higher mutation rate compared to mtDNA of younger individuals. Although they confirmed that mutations are acquired with age, no difference was found in mutational burden between AD patients and elderly controls.

Coskun and others analyzed CR of AD patients and control group brains, and identified T414G, T414C and T477C mutations, specific only for AD brains. The T414G mutation was present in 65% of the examined AD brains (Coskun et al. 2004). Regarding its location in the close proximity to the nDNA encoded transcription factor (Tfam) binding site of the promoter of the light (L)-strand of mtDNA, it has been suggested that T414G could impair the L-strand transcription and in turn heavy strand amplification (Coskun et al. 2003). Discrepant results were obtained in a prior study on more tissue samples, conducted by Chinnery and colleagues (2001). They failed to detect T414G in the healthy controls and AD patients.

An overall 63% increase in the frequency of heteroplasmic mtDNA CR mutations was reported in AD brains (Coskun et al. 2004). Some of these mutations were common to AD and control brains (T146G, T195C, T152C, A189G), however, in AD patients they were more prevalent, present at higher percentages and earlier accumulated. Intriguingly, splitting the AD patients into decade groups revealed that the 59- to 69-year age group had a 79% increase, the 70- to 79-year age group an 18% increase, and the 80-year and older a 130% increase in mtDNA heteroplasmic CR muta-

tions, in comparison to controls. As Coskun and coauthors suggest, the difference in the mutation burden between the age groups could result from acquiring one or a few somatic mtDNA CR mutations at different developmental stages (Coskun et al. 2004). Therefore, the earlier the mutational hit, the more widespread its distribution to brain cells through cell replication. Moreover, Coskun and others (2004) suggest that the mutations arising later are associated with later onset of symptoms. Above all, the severity of the dementia is suggested to be determined by the overall proportion of the brain cells that encompass a deleterious mtDNA mutation (Coskun et al. 2004). Conversly, Lin and colleagues (2002) postulated that mitochondrial function might be impaired not due to single individual mutations but to an aggregate burden of multiple ones (Lin et al. 2002).

The hypothesis stipulating that the mutations recognized as accountable for AD pathogenesis could be present starting from the earliest stages of development gained support of Smigrodzki and Khan (2005) who have combined it with their microheteroplasmy hypothesis. They postulate that if progenitor cells with accumulated mtDNA mutations give rise to differentiated cells, they have more mutations at the start, thus produce more ROS and are expected to acquire deleterious levels of microheteroplasmy after a shorter time span.

Coskun and colleagues (2004) observed a striking increase in CR mutations in the region spanning nucleotide positions 101 and 570, harboring most of the known mtDNA key elements regulating mtDNA transcription and H-strand replication. The identified CR mutations are supposed to be associated with reductions in the mtDNA L-strand ND6 mRNA and lead to mitochondrial depletion. However, Howell and others (2005) argue that many of the heteroplasmic mutations found by Coskun and coauthors (2004) to be elevated selectively in AD patients brains, occur frequently in the general population in a homoplasmic state (Howell et al. 2005).

Although the oxidative stress is well documented as intimately associated with AD, the role of mitochondria in the neurodegenerative cascade leading to AD remains unclear. Moreover, in spite of the broad evidence for altered OXPHOS in AD and a number of identified different inherited and somatic mtDNA mutations, none of them has been conclusively determined to contribute to its pathogenesis.

## INVOLVEMENT OF MITOCHONDRIAL DNA VARIATION IN PARKINSON'S DISEASE

### Nuclear genes and mictochondria

Parkinson's disease is the second most common progressive neurodegenerative condition after AD. The main pathological feature of PD is a substantial loss of dopaminergic neurons in substantia nigra, accompanied in most cases by the formation of intracellular, proteinaceous inclusions called Lewy bodies (LB) in the remaining, non-damaged nigral neurons. The major structural component of LB is α-synuclein (SNCA). Analogically to the role of Aβ in AD, SNCA aggregation is postulated as a mechanism of neurodegeneration in PD. However, it remains to be elucidated which species are pathogenic: fibrillar or protofibrillar α-synuclein forms. As some transgenic fly models suggest, the formation of LB may be a protective response against toxicity of protofibrillar α-synuclein forms (Dawson and Dawson 2003, Farrer 2006) .

It is estimated that about 90% of PD patients suffer from sporadic form of PD, while genetic factors are responsible for the remaining ca. 10% of hereditary PD cases. Mutations in at least four nuclear genes are connected with autosomal dominant mode of inheritance in PD. Those genes encode α-synuclein, ubiquitin C-terminal hydrolase-L1 (UCHL1), leucine-rich repeat kinase 2 (LRRK2) and OMI/HTRA2 protein. Mutations in three other nuclear genes: *DJ-1, PINK-1* and *PARK2* (coding respectively for DJ-1 protein, PTEN-induced kinase 1 and parkin) result in autosomal recessive PD (Abou-Sleiman et al. 2006, Greenamyre and Hastings 2004).

Studies on hereditary PD forms as well as animal and *in vitro* PD models, based on the administration of mitochondrial toxins, point to common molecular mechanisms involved in PD pathophysiology, such as mitochondrial dysfunction, oxidative and nitrosative stress, cellular transport changes, protein misfolding and impairment of protein degradation systems: ubiquitin-proteasome system (UPS) and chaperone-mediated autophagy (Abou-Sleiman et al. 2006, Eriksen et al. 2005). The three latter processes were previously often linked to familial PD, while mitochondrial impairment and oxidative/nitrosative stress constituted a more widespread phenomenon, since it was observed in all PD forms. However, recently, there is increasing evi-

dence that "divergent causes" lead to "convergent mechanisms" (Greenamyre and Hastings 2004) and all these processes influence each other through feedback and feedforward mechanisms (Abou-Sleiman et al. 2006). Both UPS and mitochondrial dysfunction lead to oxidative stress *in vivo* and *vice-versa* (broadly reviewed by Abou-Sleiman 2006).

Familial PD related genes, such as *SNCA* and *PARK2*, have been shown to influence mitochondrial function. Previous findings from animal and *in vitro* PD models regarding SNCA role suggested toxic gain of function connected with increased dosage of wild-type or with mutant protein forms, while even complete lack of SNCA did not cause detrimental effects (Eriksen et al. 2005). However, recent paper demonstrated that SNCA null mice brains are characterized by altered structure and lipid composition of mitochondrial membrane and decreased activity of complex I and III (Ellis et al. 2005).

*Drosophila* with deleted parkin shows mitochondrial pathology that precedes muscle degeneration and upregulation of the genes participating in oxidative stress response and the genes of ETC subunits (Greene et al. 2003). Parkin localization to the outer mitochondrial membrane and its anti-apoptotic activity in cellular models might implicate its role in maintaining proper mitochondrial functions (Abou-Sleiman et al. 2006).

Mutations and polymorphisms in *DJ-1* and *PINK1* genes have been recently detected in early-onset familial and sporadic PD cases, and are supposed to modulate the course of the disease (Bonifati et al. 2005, Klein et al. 2005). Experiments on human and murine neuronal cell lines demonstrated that overexpression of wild-type PINK1 (localized in mitochondria) but not its mutated form protects neurons from apoptosis (Petit et al. 2005). DJ-1 protein has a putative role in response to oxidative stress (Mitsumoto and Nakagawa 2001) and its mutated form, unlike the wild-type, prevails in mitochondria (Bonifati et al. 2003).

Newly discovered heterozygous mutation and polymorphism in the *OMI/HTRA2* gene have been found in sporadic PD patients (Strauss et al. 2005). *OMI/HTRA2* codes for a serine protease localized to mitochondrial intermembrane space that takes part in the promotion of apoptosis. OMI/HTRA2 null mice are characterized by parkinsonian phenotype, increased susceptibility to stress stimuli, mitochondrial depletion and changed mitochondrial morphology (Martins et al. 2004). Overexpression of mutant forms of this protein in a cellular model resulted in abnormal mitochondrial morphology and increased susceptibility to stress stimuli (Strauss et al. 2005).

The findings suggest that DJ-1, PINK1, PARK2 and OMI/HTRA2 are involved in protection against oxidative stress, while SNCA seems to exert an opposite effect (Abou-Sleiman et al. 2006). Full elucidation of cellular functions of abovementioned nuclear proteins might provide a link between familial and sporadic forms of the disease and highlight the crosstalk between nDNA and mtDNA genes.

### Complex I inhibition and oxidative stress in PD

Many hypotheses on PD pathogenesis converge on oxidative stress as the central and crucial event responsible for activation of a downstream cascade leading to neurodegeneration in both hereditary and sporadic PD. However, at least in sporadic PD cases, as well as in cellular and animal PD models, selective inhibition of complex I seems to be the primary event.

In PD, systemic deficiency of NADH-ubiquinone reductase of complex I has been reported in brain autopsy samples of substantia nigra (Schapira et al. 1990), platelets (Parker et al. 1989) and other tissues (Orth and Schapira 2002). A 25% decrease in complex I activity has been also confirmed in PD cybrid model, where mtDNA-less (p0) cell line was fused with platelets of sporadic PD patients (Gu et al. 1998, Swerdlow et al. 1996). Experiments on PD cybrids were the first to point to mtDNA as a potential causative factor of PD, since its transfer into cells devoid of mtDNA was able to reproduce PD-specific changes. The alterations consisted of generation of intracellular inclusions resembling LB, containing, among others, typical protein components, such as α-synuclein, ubiquitin, parkin and synphilin-1 (Trimmer et al. 2004). However, so far, the above listed changes have not been associated with a particular mtDNA mutation. That such a direct link may exist, recent findings have shown for MELAS and MERRF. In a cybrid model of these diseases particular mitochondrial tRNA mutations were demonstrated to cause increased ROS production, simultaneously leading to antioxidant factors upregulation (Vives-Bauza et al. 2006).

Further backup for a crucial role of complex I in PD has been provided by the finding that several persons abusing street drugs contaminated with 1-methyl-4-

phenyl-1,2,3,4-tetrahydropyridine (MPTP) – a known complex I inhibitor, developed PD (Langston et al. 1999). MPTP is metabolized to its active form (1-methyl-4-phenylpyridinium ion, MPP+) in glial cells, which in primates causes substantia nigra degeneration due to its selective uptake by dopamine receptors (Shimohama et al. 2003). Interestingly, synuclein null mice are resistant to MPTP induced neurodegeneration, which suggests that this protein might be an oxidative stress response modulator (Klivenyi et al. 2006).

Probably the most adequate animal model of PD has been created by chronic administration of low doses of another complex I inhibitor - pesticide rotenone to rats (Betarbet et al. 2000). This lipophilic agent readily penetrates the blood-brain barrier and unlike MPTP, causes systemic complex I inhibition, such as it is observed in PD patients. Rotenone leads to selective degeneration of dopaminergic neurons. Furthermore, the rotenone model recapitulates other PD characteristic features: Lewy bodies-like cytoplasmic inclusions, oxidative stress, microglia activation and also the behavioral symptoms: bradykinesia, rigidity and tremor-like movements (Betarbet et al. 2000). Epidemiological research and experiments on animals demonstrated the plausible connection between PD and exposition to other agricultural chemicals with a structure similar to rotenone, such as paraquat and maneb (Betarbet et al. 2002, Landrigan et al. 2005). Moreover, a role of endogenous neurotoxins such as isoquinoline derivatives is suggested in PD pathogenesis (Antkiewicz-Michaluk 2002). Abovementioned toxins are believed to operate through complex I inhibition, while downstream pathways involve oxidative stress that may lead directly or increase susceptibility to apoptosis (Betarbet et al. 2002, 2006).

Inhibition of complex I by rotenone was shown to be accompanied by increased ROS levels in isolated brain mitochondria (Hensley et al. 1998). *In vitro* chronic rotenone exposure caused oxidative damage to proteins and DNA, and reduced glutathione levels (Sherer et al. 2002). In animal and cellular models of PD, α-synuclein accumulation, DJ-1 chemical modification and translocation to mitochondria and UPS inhibition, observed after rotenone administration, turned out to be reversible upon preatreatment with an antioxidant, α-tocopherol (Betarbet et al. 2006).

Various markers of oxidative damage to DNA, proteins and lipids are detected in postmortem analysis of PD patients brains (Alam et al. 1997, Orth and Schapira 2002). PD cybrid model showed excessive ROS production, increased vulnerability to MPTP-induced apoptosis (Swerdlow et al. 1996) and elevated levels of apoptotic markers which could be reduced by administration of oxidative stress inhibitors (Onyango et al. 2005).

Nigrostriatal neurons are thought to be particularly vulnerable to oxidative stress because apart from OXPHOS, dopamine metabolism is an additional source of free radicals. $H_2O_2$ is released during physiological activity of tyrosine hydroxylase and monoamine hydroxylase – enzymes belonging to the dopamine synthesis/degradation pathway. ROS are also generated during autooxidation of dopamine (Drozak and Bryla 2005). Nitrosative stress has also been implicated in PD pathogenesis. Reactive nitrogen species, such as peroxynitrite, arise during reaction of superoxide anion and nitric oxide. This highly reactive oxidant nitrates tyrosine residues of proteins (such as α-synuclein in PD patients) and damages DNA (Giasson et al. 2000). It has also been shown to inhibit up to 50–80% the activities of complexes I, II, and V (Murray et al. 2003).

Oxidative and nitrosative stress are believed to generate somatic mtDNA mutations of a potential significance in PD pathogenesis (as discussed below).

**Mitochondrial haplogroups in PD**

The hypothesis that two crucial and widely accepted neurodegeneration mechanisms in PD: dysfunction of complex I and increased oxidative stress might stem directly from inherited mtDNA variability encouraged many scientist to search for mutations/polymorphisms that may change activity or structure of the mtDNA-encoded products.

A growing number of independent reports confirms the protective effect of haplogroup J against risk of PD (Ross et al. 2003, van der Walt et al. 2003) (Table IV). Also our preliminary results carried out in a group of 100 PD patients and 101 healthy age matched controls, indicate protective effect of haplogroup J, which is three times more frequent among controls than PD patients ($P$=0.03, Fisher's exact). Similarly, haplogroup K has also a putative protective role (Ghezzi et al. 2005, van der Walt et al. 2003).

In other studies significant differences in haplogroup pattern between PD patients and controls have not been reached. However, higher frequencies of J, K, and I haplogroups were observed among the controls, in accordance with the hypothesis that they may indeed

Table IV

Putative role of some haplogroups in PD

| Haplogroup | Postulated role | Reference (population, group sizes) |
|---|---|---|
| J | lower PD risk | Our preliminary, unpublished results, Polish population; 100 PD patients, 101 controls |
| J, K | lower PD risk | van der Walt et al. 2003, US population of European ancestry 609 PD patients, 340 controls |
| subhaplogroup J1 | lower PD risk | Ross et al. 2003, Irish population; 90 PD patients, 129 controls |
| K | lower PD risk | Ghezzi et al. 2005, Italian population; 620 PD patients, 509 and 1486 controls |
| UKJT supercluster | lower PD risk | Pyle et al. 2005, English population; 455 PD patients, 447 controls |
| all haplogroups | no differences | Huerta et al. 2005, Spanish population; 271 PD patients, 230 controls |
| JTIWX supercluster | higher PD and PD with dementia (PDD) risk | Autere et al. 2004, Finnish population; 238 PD patients, 107 controls |
| IJK group | lower PD risk, but higher PDD risk | Autere et al. 2004, Finnish population; 238 PD patients, 107 controls |

exert a protective effect (Huerta et al. 2005, Pyle et al. 2005) (Table IV). For instance, in a large cohort analysis, statistical significance for the UKJT haplogroup supercluster was obtained and associated with a 22% decrease in PD risk, but not with AD risk (Pyle et al. 2005) (Table IV). The results were similar to those of van der Walt and coauthors (2003), as the haplogroups forming supercluster UKJT are closely related and have a distinct origin than haplogroup H.

Contrary results were obtained for the Finnish population (Autere et al. 2004). The supercluster JTIWX, compared in PD, PD with dementia (PDD) and control group, was more frequent in PD patients than in healthy individuals, with the highest incidence in PDD patients. The authors proposed that a whole burden of nonsynonymous substitutions that is elevated in particular haplogroups might be responsible for PD pathogenesis. It was found that the clusters HV and KU are less variable than the clusters JT and IWX (Autere et al. 2004). However, the carriers of haplogroup I, J, or K (characterized by 10398G) showed a decreased risk for PD but an increased risk for PDD.

On the other hand, haplogroup J has been also associated with some neurodegenerative diseases such as LHON and MELAS, while haplogroup T with Wolfram Syndrome and Sudden Infant Death Syndrome (SIDS) (Brown et al. 2001, 2002, Hofmann et al. 1997, Rose et al. 2001). Moreover, haplogroup J has been reported to exert a synergistic effect with mutations causing LHON (Brown et al. 2002). A whole sequence analysis of the centenarians belonging to haplogroup J revealed many disease-associated mutations within their mtDNA (Rose et al. 2001).

In an attempt to explain the ambivalence regarding haplogroup J, Ross and colleagues distinguished between subhaplogroups J1 and J2, postulating that the different genetic background of these two branches might be the reason for contradictory results (Ross et al. 2003). In fact, the division of haplogroup J on the basis of mtDNA coding and non-coding region polymorphisms has been well documented in previous studies (Finnila and Majamaa 2001). Ross et al. did not observe any difference in the distribution of haplogroup J as a whole, only after division based on

restriction site polymorphisms they noticed that J1 prevails in aged controls, especially in women, while J2 is more common in PD patients. However, they did not suggest any SNPs that might play a key role in the putative protective effect of J1 and in the harmful effect of J2.

**mtDNA single nucleotide polymorphisms in PD**

The natural consequence of discovering the correlation between certain haplogroups and PD was an attempt to find mutations or polymorphisms directly responsible for the observed role of these haplogroups in the disease.

Many studies showed reduced frequency of the mtSNP 10398G in PD patients which is associated with J, K, and I haplogroups (Autere et al. 2004, Huerta et al. 2005, van der Walt et al. 2003). Van der Walt and others have noticed that the protective effect of 10398G is stronger in women (van der Walt et al. 2003). 10398G characterizes haplogroups J, K and I but not haplogroup T, although J and T are closely related and belong to the JTKU supercluster, while I forms another distantly related supercluster IWX. Interestingly, 10398G predominates in the African- and Asian-specific haplogroups C, D, I, L, and M (Herrnstadt et al. 2002, Torroni and Wallace 1994). This might suggest that an A to G change at the position 10398 might have arisen independently throughout human evolution (Herrnstadt et al. 2002), thus 10398G might be only a surrogate marker. Lower prevalence of the allele 10398G in the Caucasians is in concordance with the observed pattern of susceptibility to PD, more pronounced in Caucasian individuals (Muthane et al. 2001, Torroni and Wallace 1994, Van Den Eeden et al. 2003, Wallace et al. 1999).

Simon and colleagues observed a significantly higher frequency of 10398G in the controls than in PD patients, but since the analyzed population was heterogenous (comprising Hispanics, Afro-Americans, Asians and Caucasians), they eventually concluded that it might be only a bias attributable to differences in ethnicity (Simon et al. 2000).

In contrast, Otaegui and coauthors proposed the 10398G allele as a risk factor for PD since it prevailed among PD patients of Basque origin (Otaegui et al. 2004). Nonetheless, the authors observed this effect only in a relatively small group of the Basques but not in the general Spanish population (Otaegui et al. 2004). Another explanation for such an outcome could be a different genetic background of the Basques, which has been well documented.

Longevity-associated mtSNP, 9055A, was found at an increased frequency among healthy women in comparison with PD group (van der Walt et al. 2003) (Table V). The allele 9055A has been connected with reduced sperm motility (Holyoake et al. 2001). Other research suggest that mtDNA variability depends on climatic adaptation in humans, with the highest number of changes found in ATP6 gene in colder climates (Mishmar et al. 2003). Thus, some mtSNPs (like 9055A) might decrease the coupling of mitochondrial

Table V

List of SNPs/mutations potentially involved in PD

| SNP/mutation | Postulated role | Reference |
|---|---|---|
| 10398G | decreases PD risk<br>increases PD risk<br>no difference observed | Autere et al. 2004, Huerta et al. 2005, van der Walt et al. 2003<br>Otaegui et al. 2004<br>Ghezzi et al. 2005, Simon et al. 2000 |
| 9055A | decreases PD risk | van der Walt et al. 2003, only in women |
| 4216C | increases PD risk<br>no difference observed | Brown et al. 1996, Kirchner et al. 2000 - only in men, Ross et al. 2003<br>Huerta et al. 2005 |
| 13708A | decreases PD risk – observed only in the group ≤ 70 years | van der Walt et al. 2003 |

electrochemical gradient with ATP synthesis as a result of diminished activity of ATP synthase, as suggested by Mishmar and colleagues (2003). Then some physiological activities might be impaired (like semen motility), while e.g. the heat production and also basal metabolic rate would rise, at the same time increasing the adaptive advantage and chances of survival in arctic zones. Therefore, although 9055A polymorphism might be connected with a slightly decreased activity of ATP6, it may give yet unknown advantage and also protect from developing PD, as a result of reduced ROS production.

Apart from the above described 4336G, the 4216C allele within ND1 gene was reported to increase susceptibility to PD (Brown et al. 1996, Kirchner et al. 2000) (Table V). Nonetheless, Kirchner and coauthors (2000) detected this only in men. Ross and others found 4216C to be twice more frequent in PD patients than in the controls, but as an independent study showed, this mtSNP had a similar frequency in young controls (18–45 years) (Ross et al. 2003). Some authors did not observe any difference in 4216C distribution between PD patients and healthy individuals (Huerta et al. 2005).

Besides, T4216C, G13708A, and A4917G (located in: ND1, ND5, and ND2, respectively) are associated with LHON as secondary mutations, unable to cause a disease themselves but occurring simultaneously with the primary (causative) mutations and thus they may modify the pathogenesis (Johns and Berman 1991). A slight, statistically insignificant increase in secondary LHON mutations in PD patients was reported, however only when data for different ethnic populations were pooled together (Simon et al. 2000). In the Irish population, the frequency of four LHON linked pathogenic point mutations (primary: G3460A and the secondary: T3394C, T4160C, A4136G) in both PD and the controls has turned out to be low enough that their potential role in PD pathogenesis might be excluded (Ross et al. 2003).

Although sequencing of the entire mitochondrial genome seemed promising, no causative mutations for PD nor protective SNPs were identified, predominantly due to an insufficient number of cases analyzed (Brown et al. 1996, Simon et al. 2000, Vives-Bauza et al. 2002). For instance, sequencing of the entire mtDNA from substantia nigra of 8 PD patients and 9 controls revealed a few mutations but none of them was exclusively specific for PD (Vives-Bauza et al. 2002). Analysis of the aggregate burden of mutations also did not demonstrate any significant differences between controls and PD patients. The only differences of a potential significance referred to a few known polymorphisms, but none of them has been so far related to any disease. Three of them were connected with cytidine insertions in nucleotide positions 309 and 315 (C309CCC, C309CC, C315CC) within extremely polymorphic poli-C tract in the hypervariable region 2 (HV2) of the CR. Another change, C3106del (16S rRNA), prevailing in PD individuals had been previously reported as a common polymorphism.

The results of some of the above cited association studies are contradictory. Inconsistencies might arise due to some obvious factors, like inappropriately suited control groups, insufficient number of analyzed individuals or genetic heterogeneity.

In case of haplogroup studies some of the mtSNPs might have arisen independently during evolution, so they could be present on a background of unrelated or weakly related haplogroups. Thus, in such cases further investigation is needed to test whether the observed effect is connected with a particular haplogroup as a whole (close characterization of a particular haplogroup should be carried out by evolutionary approach) or rather with a specific SNP/mutation that changes functional properties of a protein or RNA .

Furthermore, in the case of PD, there has been considerable evidence that gender might predispose or protect from developing the disease. It is supposed that men are more prone to develop PD (Van Den Eeden et al. 2003). Indeed, neuroprotective role of estrogens has been suggested in PD, which opens new possibilities of the treatment (Manthey and Behl 2006, Morale et al. 2006).

It also seems that in order to definitely confirm the association of an analyzed mtSNP/mutation with PD risk and exclude the effect of a “surrogate mutation”, it would be necessary to sequence the whole mitochondrial genome in a sufficiently big and representative group.

#### Somatic mtDNA mutations in PD

Analysis of somatic mutations, especially in brain, is more problematic than in the case of the constitutive ones. Measuring the level of somatic mutations in substantia nigra neurons is a challenging task, due to the presence of other tissue admixture in brain

homogenates and/or advanced degeneration process, that might lead to up to 80% loss of substantia nigra neurons and, consequently, to the underestimation of the mutation number (Cantuti-Castelvetri et al. 2005, Simon et al. 2004).

Simon and coauthors performed clonal sequencing of the ND4 subunit of complex I of frontal cortex and substantia nigra samples from PD patients, aged matched controls and healthy individuals at different ages (Simon et al. 2004). It allowed identification of low frequency mutations. The authors confirmed a previous findings from the brain samples of AD patients that each individual mutation is present at a low level, but together they reach high number (Simon et al. 2001). The differences between the mutation burden in frontal cortex and substantia nigra of PD patients and age-matched healthy individuals were not statistically significant, although they were slightly higher for the PD group. However, the authors noticed that point mutations burden in the frontal cortex of healthy individuals increases with age, reaching the highest level of 162.4 per million base pairs in the elderly subjects in comparison to the two groups of young controls (<10 years old and between 12–24 years old). Substantia nigra mutation burden was similar in all age groups and, at the same time, higher than in the frontal cortex.

Smigrodzki and coauthors sequenced clones of 7 mtDNA-encoded subunits of complex I from the frontal cortex of 6 PD patients and 6 healthy controls (Smigrodzki et al. 2004). The mutation frequencies of the complex I genes, cytochrome b and tRNA genes calculated together and of the CR (excluding known mtSNPs and high-level heteroplasmic mutations) were 59.3; 66.1; and 640 mutations per million bps, respectively. No difference was found in the aggregate mutation burden between PD patients and the control group.

Apart from point mutations, other types of somatic mtDNA changes may play a role in PD pathogenesis (Bender et al. 2006, Mawrin et al. 2004). Substantia nigra contains the highest number of mtDNA deletions in the whole body, which might result from the prooxidative dopamine metabolism (Bender et al. 2006).

In the aged subjects and PD patients these deletions reach high levels (up to 50%) that might be phenotypically significant and their elevated amount correlates with decreased activity of cytochrome c oxidase. However, in PD individuals the level is only slightly higher than in the controls.

## CONCLUSIONS

The major risk factor for sporadic AD and PD still remains age. The frequent co-occurrence of these two conditions implicates some similarities in the pathogenesis. So far, it has been proposed that oxidative stress (independently of its origins – environmental factors, genetic predisposition, senescence) and mitochondrial dysfunction may be a link between PD and AD. In this paper we have focused on the putative impact of mtDNA changes and presented a spectrum of shared (such as 4336G and 10398A) and distinct gene variants observed in both diseases.

However, one can not think of mitochondria in isolation, as mitochondrial dysfunction in AD and/or PD could be also a result of the nuclear genome mutations. The mitochondrial respiratory chain complexes comprise mitochondrion- and nucleus-encoded subunits. The nucleus encodes ca. 98% of mitochondrial respiratory chain polypeptides, synthesized in the cytoplasm and translocated into the mitochondrion (Chinnery and Schon 2003, Schapira 2002). The import machinery proteins and the respiratory chain assembly proteins are the products of nDNA expression (Chinnery and Schon 2003). In addition, mtDNA remains dependent on the nucleus for numerous control and catalytic proteins, like the mitochondrial DNA polymerase γ (POLG1), factors sustaining an appropriate balance of free nucleotides within the mitochondrion (TP, TK, DGK, ANT1), the substantial factors requisite for intramitochondrial transcription and translation (TFAM, TFBM1, TFBM2) (Chinnery and Schon 2003). Therefore, mutations in nuclear genes coding for components involved in OXPHOS and maintaining its functioning should also be considered.

Identification of mitochondrial basis of neurodegenerative disorders could result in novel treatment methods improving various mitochondrial functions, targeted to mitochondrial permeability transition, or exerting antioxidant activity.

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