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The Impact of Mitochondrial DNA and Nuclear Genes Related to Mitochondrial Functioning on the Risk of Parkinson's Disease

Katarzyna Gaweda-Walerych* and Cezary Zekanowski

Laboratory of Neurogenetics, Mossakowski Medical Research Centre, Polish Academy of Sciences, Pawinskiego 5 str., 02-106 Warszawa, Poland

Abstract: Mitochondrial dysfunction and oxidative stress are the major factors implicated in Parkinson's disease (PD) pathogenesis. The maintenance of healthy mitochondria is a very complex process coordinated bi-genomically. Here, we review association studies on mitochondrial haplogroups and subhaplogroups, discussing the underlying molecular mechanisms. We also focus on variation in the nuclear genes (*NDUFV2, PGC-1alpha, HSPA9, LRPPRC, MTIF3, POLG1,* and *TFAM* encoding NADH dehydrogenase (ubiquinone) flavoprotein 2, peroxisome proliferator-activated receptor gamma coactivator 1-alpha, mortalin, leucine-rich pentatricopeptide repeat containing protein, translation initiation factor 3, mitochondrial DNA polymerase gamma, and mitochondrial transcription factor A, respectively) primarily linked to regulation of mitochondrial functioning that recently have been associated with PD risk. Possible interactions between mitochondrial and nuclear genetic variants and related proteins are discussed.

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1. INTRODUCTION

Parkinson's disease (PD) is the second most common progressive neurodegenerative disorder, clinically defined by cardinal motor features: tremor, rigidity, bradykinesia and postural instability [1]. The symptoms appear upon the loss of approximately 50% of *substantia nigra* (SN) dopaminergic (DA) neurons resulting in a depletion of striatal dopamine by about 70-80%, indicative of compensatory mechanisms enabling "normal" functioning despite the ongoing deterioration [2, 3]. Also other neuronal populations in the brain stem and subcortical and cortical regions are affected in PD [4]. Additionally, PD is associated with non-motor symptoms that can co-occur or precede the motor manifestations by many years [5]. They comprise cognitive and psychiatric problems, impaired olfaction, sleep disturbances, and autonomic insufficiency [6, 7]. PD is clinically heterogeneous, with two major subtypes associated with different prognoses: the tremor- prevalent and the "postural imbalance and gait disorder" (PIGD) form, the latter aggravating more rapidly [8]. The pathological hallmark of PD are proteinaceous aggregates in neuronal perikarya (Lewy bodies, LBs) and processes (Lewy neurites, LNs) containing mainly misfolded α-synuclein (SNCA) [4]. They are observed in most PD cases with the exception of some genetically caused ones (e.g. *PARK2* mutations).

Despite their apparently different causative factors and possibly also the course of pathogenesis, most of the sporadic PD forms are difficult to be distinguished from the genetic ones at the clinical level [8, 9]. Only about 10% of PD cases arise due to mutations in known genes. Mutations in *PARK2* (coding for parkin), *PARK6* (coding for PTEN induced kinase 1, PINK1), and *PARK7* (coding for DJ-1) are responsible for autosomal recessive PD forms, while *PARK1* (coding for α-synuclein, α-SNCA) and *PARK8* (coding for leucine-rich repeat kinase 2, LRRK2) mutations cause autosomal dominant PD. The remaining cases are idiopathic, however, currently unknown genetic background could not be ruled out in those cases.

PD pathogenesis involves complex interactions between individual inherited genetic background, physiological aging, and the environment. At present aging is considered the most important PD risk factor connected with a decline in the efficiency of numerous cellular processes and aggravated by possible environmental insults, e.g., exposure to mitochondrial toxins. Additionally, male gender seems to predispose to PD [10].

Analysis of sporadic and genetically caused PD in humans, in animal and *in vitro* PD models enabled identification of major molecular mechanisms involved in PD pathogenesis, namely, oxidative stress, mitochondrial dysfunction, inflammation, impairment of cellular degradation systems, (including micro- and macroautophagy, chaperone-mediated autophagy, and the ubiquitine-proteasome system), defective protein folding, and cellular transport abnormalities. These processes are interdependent, which makes it difficult to determine the primary cause of the neurodegeneration.

Mitochondrial dysfunction has been implicated in both sporadic and genetically caused PD, in patients as well as in numerous PD models; reviewed in [11-13]. Mitochondrial

*Address correspondence to this author at the Laboratory of Neurogenetics, Mossakowski Medical Research Centre, Polish Academy of Sciences, Pawinskiego 5, 02-106 Warszawa, Poland; Tel: +48 22 6086485; Fax: +48 22 668 55 32; E-mail: kasiawal@libero.it

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DNA (mtDNA) encodes 13 proteins of oxidative phosphorylation, two rRNAs and 22 tRNAs. The remaining ETC subunits and approximately 1000-1500 other mitochondrial proteins are encoded by nuclear DNA (nDNA) [22]. Therefore, proper mitochondrial functioning requires a coordinated interplay among factors encoded by both nuclear and mitochondrial DNA.

The products of genes involved in the pathogenesis of rare genetic PD cases have turned out to be involved in the maintenance of mitochondrial function, reviewed in [12-15]. To date, parkin, PINK1, and DJ-1 have been implicated in mitochondrial autophagy (mitophagy), where they likely operate in a network of reciprocally regulated pathways [16, 17]. Moreover, parkin and PINK1 seem to be crucial for mitochondrial biogenesis, transport, and dynamics [12-14, 18, 19]. Also LRRK2 and SNCA take part in mitochondrial dynamics and homeostasis [20, 21]. All these processes are engaged in the maintenance of healthy mitochondria, which seems especially important in stress conditions.

Here, we focus on common variation of mtDNA and nDNA as a potential source of functional changes that could affect mitochondrial performance and thus influence PD risk. We also discuss possible interactions between the two genomes and their potential significance for future design of PD association studies.

The genes coding for the mammalian mitochondrial proteome consisting of about 1000–1500 distinct proteins [22, 23] are all potentially plausible candidates for PD association studies. For this reason our report is limited to those encoding the main mitochondrial biogenesis/maintenance factors (*NDUFV2, PGC-1alpha, HSPA9, LRPPRC, MTIF3, POLG1, TFAM, TFB1M, TFB2M*) and for which association studies/mutational screening have been performed. These genes only recently have been linked to PD pathogenesis and thus have not been deeply studied. We have searched extensively the public databases, including NCBI (National Center for Biotechnology Information) and PDGene (a database of Parkinson's disease association studies) [24]. The role of genetic variation in *PARK* genes and of their products (parkin, PINK1, DJ-1, SNCA, LRRK2) in mitochondrial physiology and PD pathogenesis have been reviewed extensively elsewhere [12-14, 25, 26] and is not the subject of this review.

2. WHAT CAUSES THE SELECTIVE VULNERABILITY OF PD-AFFECTED NEURONS TO MITOCHONDRIAL DYSFUNCTION AND OXIDATIVE STRESS?

A common denominator of neurons degenerating in PD are long, thin axons with little or no myelination [27]. Gene expression profiling studies indicate that *substantia nigra* A9 DA neurons are more metabolically active, with up-regulation of genes involved in energy metabolism, electron transport and those coding for mitochondrial proteins, than the A10 DA neurons of ventral tegmental area (VTA) that are relatively well preserved in PD [28-30]. These characteristics make the SN DA neurons highly dependent on properly regulated mitochondrial function: efficient oxidative phosphorylation (OXPHOS) providing ATP, mitochondrial fusion and fission, transport between cell bodies and long axon terminals, biogenesis and mitophagy. In addition, the selective vulnerability of the SN DA neurons preferentially affected in PD could also stem from:

1). sustained cytosolic and mitochondrial Ca^{2+} overload driven by unique to *substantia nigra* voltage-dependent L-type Ca^{2+} channels contributing to increased reactive oxygen species (ROS) generation [31, 32];

2). higher oxidative stress caused by prooxidative dopamine metabolism, in addition to the OXPHOS-derived ROS [33]. ROS are generated during dopamine autooxidation while H_2O_2 is produced during physiological activity of tyrosine hydroxylase and monoamine oxidase – enzymes of dopamine biosynthesis and degradation pathways;

4). the highest frequency of mtDNA deletions relative to other brain regions, possibly as a result of oxidative damage induced by ROS derived from OXPHOS, dopamine metabolism, and Ca^{2+} overload [34].

3. MITOCHONDRIAL DYSFUNCTION IN PD PATHOGENESIS

Mitochondria are crucial in energy generation, ROS production, Ca^{2+} cellular homeostasis, apoptosis, and numerous metabolic pathways including steroid and heme biosynthesis, and β-oxidation of fatty acids. Thus, it is not surprising that mitochondrial failure is implicated in a wide variety of diseases, generally involving organs with a high-energy demand such as brain, heart and skeletal muscles [35, 36].

One of the earliest pieces of evidence of mitochondrial dysfunction in PD was the discovery that the complex I (CI) NADH:ubiquinone oxidoreductase activity was decreased in platelets from patients with sporadic PD [37]. Those results were confirmed in midbrain *substantia nigra*, frontal cortex, skeletal muscles, and platelets of PD patients and in cybrid models of PD [38-47]. Moreover, analysis of cybrids obtained by fusion of rho0 cells lacking mtDNA and platelets from sporadic PD patients showed that mitochondria from the PD platelets are sufficient to reproduce parkinsonian-like changes at the cellular level, including the PD hallmarks such as LBs - like proteinaceous inclusions containing α-synuclein, ubiquitin, parkin and synphilin-1 [48]. Furthermore, since Langston *et al.* described acute PD development in drug addicts after exposure to a complex I inhibitor, 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine (MPTP), in the early 1980s [49], administration of complex I inhibitors (MPTP, rotenone, paraquat, maneb, etc.) has become a standard approach in animal and cellular PD models reproducing PD pathology to different extents [50-55]. The rotenone-based animal PD model is still among the most faithful ones, recapitulating Lewy body-like cytoplasmic inclusions, increased oxidative stress, microglia activation, and behavioral symptoms, such as bradykinesia, stiffness and tremor-like movements [51]. Rotenone crosses the blood-brain barrier (unlike MPTP which is selectively taken up by dopamine receptors) causing systemic inhibition of complex I and degeneration of SN DA neurons. A role of endogenous neurotoxins (dopamine metabolites - tetrahydroisoquinolines and their derivatives with neurochemical characteristics similar to MPTP) has been also proposed in PD pathogenesis, reviewed in [56]. Moreover, numerous epidemiological studies have shown an association between PD and exposure to

complex I inhibitors, used as pesticides/insecticides in agriculture [57].

However, the hypothesis that mitochondrial CI deficiency is a causal factor of PD has been challenged recently. Selective inactivation of the nucleus-encoded CI subunit of NADH:ubiquinone oxidoreductase, iron-sulfur protein 4 (Ndufs4), in neurons and glia of knockout mice affected primarily non-DA neurons of the olfactory bulb, cerebellum, and vestibular nuclei, without *substantia nigra* degeneration [58, 59]. The Ndufs4 loss in mice led to fatal encephalomyopathy with growth retardation, ataxia, unsteady gait, and blindness, recapitulating some features of Leigh syndrome [58, 60]. As subsequently demonstrated a conditional *Ndufs4* knockout in DA neurons in mice resulted in only a small decrease in DA neurons, with striatal innervation preserved. Although the DA release was impaired and the level of DA metabolites increased, no symptoms of parkinsonism were observed. In addition, the knockout mice were more vulnerable to the neurotoxin MPTP [61].

Nonetheless, it is worth noting that induced mitochondrial dysfunction in DA neurons of transgenic mice, results, in most cases, in parkinsonian-like phenotypes. For instance, a conditional SN-specific deletion of both mitochondrial transcription factor A (TFAM) alleles in mice leads to progressive motor dysfunction with adult onset, formation of intraneuronal inclusions, striatal dopamine depletion, death of DA neurons, abnormal mitochondrial morphology, reduced mtDNA expression, and respiratory chain deficiency [62-64]. In another model, selective overexpression of a mitochondria-targeted restriction enzyme PstI introducing DNA double-strand breaks in DA neurons resulted in mtDNA depletion, a progressive neurodegeneration of the SN DA neurons, striatal dopamine depletion, and a motor phenotype responsive to L-DOPA treatment [65]. Finally, overexpression of mutant twinkle, a helicase essential for mtDNA maintenance and replication, in DA neurons in mouse, causes mtDNA deletions, degeneration of SN DA neurons, and some PD-like behavioral deficits [66].

The differences in the outcome between the targeted disruption of TFAM or twinkle versus Ndufs4 in DA neurons could be explained by the different molecular mechanisms and the compensatory potential related to the different causes of the mitochondrial dysfunction. In the case of TFAM or twinkle, mtDNA damage seems to be the primary source of mitochondrial dysfunction. In contrast, upon the *Ndufs4* gene disruption, the cause of the mitochondrial impairment is CI deficiency, possibly due to CI assembly failure and instability [58]. Ndufs4 is one out of at least 45 different subunits forming CI, the largest respiratory chain complex encoded both by nuclear and mitochondrial DNA. As it has turned out subsequently, CI activity is only partially compromised *in vivo* in the *Ndufs4* knockouts, due to compensatory formation of respiratory supercomplexes with mitochondrial complex III [61, 67]. Thus, it could be speculated that the Ndufs4-related mitochondrial dysfunction is easier to compensate than TFAM or twinkle-related impairment.

4. MITOCHONDRIAL HAPLOGROUPS AND PD RISK

The mtDNA is inherited exclusively maternally as a haplotype. Based on phylogenetic relationships, the mtDNA haplotypes can be classified into subhaplogroups, haplogroups and haplogroup clusters characterized by a set of specific polymorphisms. An analysis of mtDNA haplotypes has enabled creation of a human migration map and trace the human origins to Africa, where the most ancient and variable lineages occur: L0, L1, L2 and L3 [68]. They evolved into macrohaplogroups M and N, that subsequently left Africa to colonize Eurasia. In Europe, nine mtDNA lineages prevail: H, I, J, K, T, U, V, W and X, forming four clusters: HV, UK, WIX and TJ. Haplogroup H is the most common one, in spite of being relatively young in evolution [69-73]. The haplogroup distribution on Earth shows highly specific regional variation that, according to some researchers, cannot be explained merely by the founder effect [68, 74-77].

An exclusively maternal mode of inheritance has been observed in few PD pedigrees [78, 79]. Only cybrids carrying mtDNA from the maternal descendants of PD patients (asymptomatic or manifesting PD) had a lower activity of complex I, increased ROS levels and activities of ROS scavenging enzymes, and altered mitochondrial morphology [78]. In contrast, a recent large case-control study of 168 multiplex PD families found no evidence of maternal inheritance in familial PD [80].

Importantly, no inherited causative mtDNA mutations have been identified through mtDNA sequencing in PD patients [81-83]. Thus, it was proposed that common mitochondrial DNA variation, comprising inherited and somatic mutations, could influence the OXPHOS efficiency, mitochondrial functioning, and thereby modify the PD risk. Numerous association studies have addressed this issue producing ambiguous results [84-93]. In parallel, *in vitro* and *in silico* studies allowed the formation of a hypothesis that facilitated interpretation of discordant outcomes of the association studies.

4.1. Do "Partially Uncoupling" mtDNA Lineages Decrease PD Risk?

The hypothesis posits that the JTKU cluster and its specific sublineages (U4, U5a1, K, J1c and J2) could exert a protective effect in PD and other diseases, such as Alzheimer's disease (AD), diabetes, and aging due to the presence of sub/haplogroup-specific polymorphisms that decrease the mitochondrial coupling. In such conditions, ATP but also ROS production is decreased, while more energy dissipates as heat [68, 94-97], (Fig. **1**). To date, Montiel-Sosa *et al.* have found that, within the UK cluster, sperm carrying subhaplogroups U4, K and U5a1 exhibit lower viability and motility (parameters directly related to OXPHOS coupling efficiency and ATP generation) than the U5b sperm [94, 97]. *In silico* studies pinpointed potentially "partially uncoupling" polymorphisms within subhaplogroups J1c and J2 [95, 97]. These results underline functional heterogeneity even within a given haplogroup that could account for the discrepant results obtained in association studies and underscore the need to stratify haplogroups into subhaplogroups [93]. Interestingly, it has also been found that lineages carrying "partially uncoupling" mtDNA variants (U5a and U4) are enriched in Northern Europe, and could have played a role in the adaptation to cold climates by more efficient heat genera-

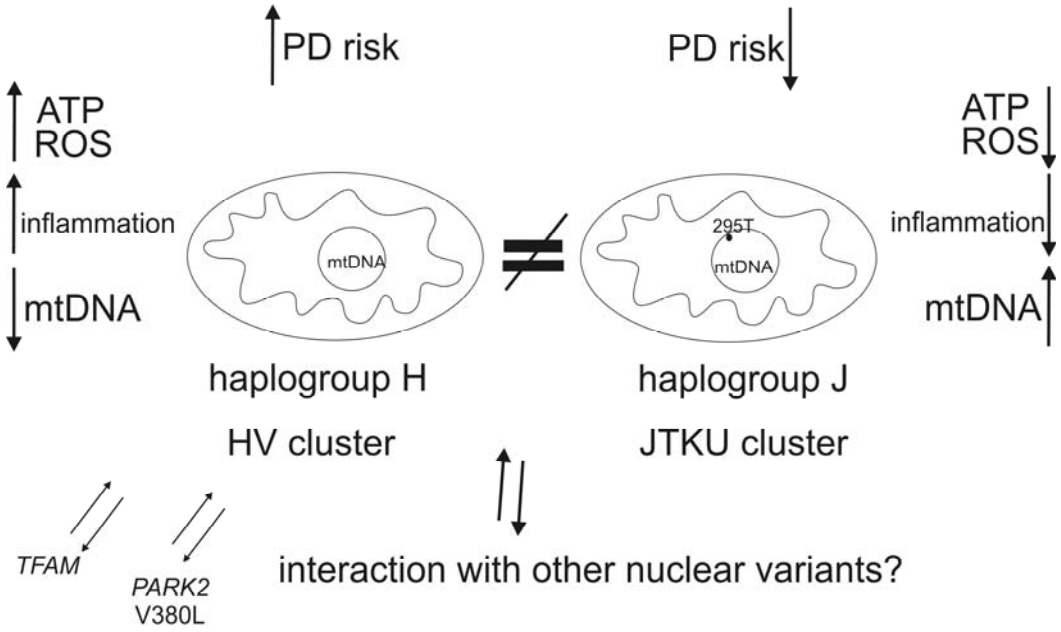

Fig. (1). mtDNA common variation and PD risk.

JTKU cluster and specific sublineages within it (U4, U5a1, K, J1c and J2) are postulated to decrease PD risk due to the presence of sub/haplogroup-specific polymorphisms that lead to a less efficient coupling efficiency. In such conditions, ATP but also ROS production is decreased, while relatively more energy dissipates as heat. Also the influence of non-coding SNPs (such as 295T within the TFAM binding site) should be taken into account (see paragraph 4.5). On the other hand, the most common European haplogroup H (present in about 40% of Caucasians) has been demonstrated to increase PD risk in the recent meta-analysis. It has been associated with higher levels of inflammation biomarkers than haplogroup U. It is plausible that mtDNA background interacts with nuclear variants. For example, *PARK2* and *TFAM* SNPs seem to increase PD risk on the HV cluster background (see paragraph 5.5).

tion [97]. In addition, cytochrome b gene has been shown to have a higher ratio of non-synonymous vs. synonymous (NS/S) variants in European than African mtDNAs. Although purifying selection is regarded the major driving force in the human mtDNA evolution [95, 98], the above results suggest that the role of adaptive selection increased upon human migration from Africa to the moderate and arctic climates of Eurasia [95]. They also explain the specific geographic pattern of haplogroups [68].

The discussed hypothesis, however, has been challenged by other researchers [98-101]. For instance, Sun *et al.* did not find differences in the NS/S ratio between haplogroups from three distinct climatic regions, proposing instead that the specific haplogroup distribution on Earth should be attributed to genetic drift and purifying selection [98], while Kivisild *et al.* found gene-specific differences in the NS/S ratio between mtDNA haplotypes even in the same geographic region [101]. Moreover, no functional respiratory differences between Arctic- and African-specific mtDNA lineages, expected from the hypothesis in question, were found in a cybrid model, with even better OXPHOS coupling observed in cybrids carrying the arctic ones [99].

4.2. Haplogroup J – Less ROS, More Protection?

Despite the controversy regarding the hypothesis discussed above, some studies have found an association between the JTKU cluster or particular haplogroups within it and a decreased PD risk [87-90, 93] or reported such a trend for haplogroup J [92]. In particular, we and others have found that sublineages U4, U5a1, K, J1c, J2 (collectively) proposed to be partially uncoupling are associated with a decreased PD and AD risk in Polish and Russian Tatar cohorts [90, 93, 102].

In addition, haplogrup J has been associated with longevity [103-106]. It has also been shown to protect from osteoarthrithis, where oxidative damage is strongly implied in the pathogenesis [107, 108]. As demonstrated by a growing number of functional studies, the beneficial effect of haplogroup J seems to arise from a lower systemic oxidative and nitrosative stress due to less efficient ATP generation in comparison with other haplogroups [109-111], (Fig. **1**). Consistent with this notion, various cybrid models using different lines of rho0 cells have demonstrated lower ATP production and ROS levels for haplogroup J cybrids in comparison to non-J or haplogroup H cybrids [112, 113]. Interestingly, haplogroup J cybrids grew faster than H cybrids, which could be related to higher lactate levels indicating enhanced glycolysis rate in those cybrids [113].

Similar observations have been made for human-derived tissues, despite potentially confounding variation of the nuclear genome [110]. Martinez-Redondo *et al.* have shown lower maximum oxygen consumption (VO_2max) rates and lower oxidative damage in individuals carrying haplogroup J [110]. In addition, Fernandez-Moreno *et al.* have reported that subjects harboring haplogroup J have decreased mRNA levels of inducible nitric oxide synthase (iNOS), lower production of nitric oxide (NO) in cultured chondrocytes, and longer telomeres in leukocytes, independently of age and

gender [111]. Although oxidative stress has been suggested as a causative factor of telomere shortening, telomere length analyses in PD patients are inconclusive [114-118].

Recently, mitochondrial haplogroups have been reported to modulate global DNA methylation levels, found higher in peripheral blood DNA of J - carriers in comparison with non-J ones [112]. The significance of the latter finding remains to be clarified.

In some specific disorders, however, haplogroup J has detrimental effects, as it increases the penetration of mild mtDNA complex I mutations associated with Leber's hereditary optic neuropathy (LHON) [119, 120]. The partially uncoupling OXPHOS variants have therefore been proposed to act synergistically with mild mtDNA complex I mutations, lowering the ATP level below the physiological threshold and thus leading to energetic deficit and blindness manifestation [96].

4.3. Haplogroup H – A Pro-oxidative Haplogroup?

On the other hand, the most common European haplogroup H and the HV cluster have been proposed to predispose to certain neurodegenerative diseases, such as PD and AD due to the most efficient OXPHOS coupling among the European haplogroups, and the consequent increased ATP and ROS production [96], (Fig. **1**). For this reason, haplogroup H is thought to be advantageous for organs with a high ATP demand such as brain, liver, and heart [121] and has been shown to exert a protective effect in temporarily compromised OXPHOS as occurs in sepsis and stroke [122, 123]. Indeed, functional studies have demonstrated that haplogroup H carriers have a higher VO_2max and increased ATP and oxidative stress levels in comparison with haplogroup J carriers [109, 110, 112, 113]. Also patients with Huntington's disease carrying haplogroup H display higher ATP levels than non-H individuals [121]. The association studies supporting haplogroup H-related increased PD risk have low statistical power [55, 90], with the exception of a recent one including meta-analysis [124]. Similar evidence has been also provided for AD [125, 126].

Despite the elegance of the hypothesis on beneficial/detrimental effects of "partially uncoupling vs. efficiently coupling" haplogroups (respectively) in neurodegenerative diseases, consistent evidence is lacking. Some studies found no association of mitochondrial haplogroups with the risk of PD [80, 91]. Likewise, some functional studies failed to corroborate the postulated bioenergetic differences between the "partially uncoupling" and "efficiently coupling" haplogroups such as J, T, K and H [127-129], while others do not match the hypothesis [73]. For example, K cybrids show higher ATP production than haplogroup H cybrids and comparable ROS levels [73].

Contradictory functional results have also been obtained for cybrids carrying Asian mitochondrial haplogroups, many of which had been previously associated with the risk of various disorders including PD, AD and diabetes [130-135]. One study on Taiwanese population-derived cybrids reported that haplogroup B4b cybrids had a significantly lower oxygen consumption rate and higher mitochondrial membrane potential compared to F1a, B5, D5a, D4a, and N9a cybrids, but at the same time they were more susceptible to H_2O_2-induced oxidative stress than F1a, D4a, or N9a cybrids [135]. A N9a cybrid had a higher oxygen consumption and H_2O_2-challenged viability compared to B4b, F1a, B5, D5a, and D4a [135]. On the other hand, a Korean study did not detect any differences in ATP and ROS levels, mitochondrial membrane potential, and viability among analyzed cybrids [134]. However, microarray gene expression profiling showed that haplogroups N9a, D5 and F did influence the expression pattern of both mitochondrial and nuclear genes involved in cellular energetics [134]. For example, haplogroup N9a cybrids featured up-regulation of the oxidative phosphorylation pathway and down-regulation of glycolysis and gluconeogenesis signaling, as compared to haplogroup F ones [134], suggesting that variations in mtDNA can affect the expression of nuclear genes regulating mitochondrial functioning or cellular energetics.

4.4. Changes of mtDNA Levels in PD

Although some data indicate that the amount of mtDNA decreases during aging in humans and animal models, they are generally inconclusive [136-143]. No systematic effort to correlate the mtDNA level with PD pathogenesis and progression has been undertaken to date. Cybrids containing mtDNA from sporadic PD patients demonstrated decreased mtDNA and mtRNA levels [144, 145]. Interestingly, the MPP(+) ion (1-methyl-4-phenylpyridinium), apart from complex I inhibition, has also been proposed to destabilize mtDNA D-loop structure, inhibit mtDNA replication and decrease its content in cultured cells [146, 147]. Also early onset (EOPD) patients carrying *PARK2* mutations display a 22% decrease in mtDNA level [19]. Moreover, in *substantia nigra* of elderly people up to 80% of mtDNA molecules carry deletions [34, 148], suggesting that mtDNA and the mitochondrial network can be damaged more promptly there than in other brain regions, possibly due to prooxidative dopamine metabolism.

The mtDNA copy number has been proposed to be regulated by ROS levels. Low-level chronic oxidative stress has been shown to increase the copy number *in vitro* and *in vivo*, and in mice cybrids [149-151]. Thus, the "partially uncoupling" sublineages within the UKTJ cluster could be expected to display higher mtDNA levels in comparison with the prooxidative haplogroup H [152]. However, the results obtained so far are inconsistent. The amount of mtDNA has been reported either lower for K cybrids or higher/unchanged for J cybrids in comparison with haplogroup H cybrids [73, 113, 152].

4.5. Do Control Region Variants Contribute to Haplogroup-related PD Risk?

The studies on the role of mtDNA variation in PD focused mainly on the coding-sequence polymorphisms potentially influencing encoded RNA or protein products. Recently the attention has turned to, so far neglected, non-coding SNPs, occurring within the control region, which comprises mtDNA promoters and origins of replication – the binding sites for the mtDNA replication and transcription machineries [153, 154]. For instance, the mtSNP 295T unique to haplogrup J is localized within the mitochondrial

transcription factor A binding site. Haplogroup J cybrids had higher mtDNA level, increased TFAM binding and mtDNA transcription level *in vitro* in comparison with haplogrup H cybrids [152]. mtSNP 295T could be potentially responsible for these phenomenon. However, no differences were found in mitochondrial RNA (mtRNA) levels between cybrids with the haplogroups J and H [152]. It is plausible that compensatory normalization of mitochondrial gene expression in response to changed mtDNA levels could account for this observation [145]. It is also known that increased mtDNA level is not necessarily coupled with increased mRNA level [152]. Interestingly, lower levels of mtRNA transcripts have been observed in K cybrids in comparison with H cybrids [73, 152].

The above results indicate that a dysfunction of mtDNA replication and/or transcription may be a common feature in both sporadic and genetic PD forms. It is conceivable that the higher mtDNA level and possibly also transcription efficiency in haplogroup J carriers (if confirmed in future studies) could favor a more efficient compensatory mechanism when mitochondrial functioning is compromised in the course of PD and therefore slow down PD progress, shifting the threshold towards functional mitochondria (Fig. **1**).

The inconsistent outcomes of studies addressing physiological differences among mtDNA sub/haplogroups indicate that a) some mtDNA lineages may be functionally significant while others not, or/and b) the nuclear genome may compensate for subtle functional differences between mtDNA lineages [134]. All in all, there is a need of an integrative approach combining well-designed association studies with functional ones, simultaneously analyzing the mtDNA haplotype and its physiological properties in human subjects/animal/*in vitro* models, in conditions related to health and disease.

4.6. mtDNA Somatic Mutations

Mitochondrial dysfunction can also result from accumulation of somatic mtDNA mutations throughout the lifespan, particularly detrimental for post-mitotic cells such as neurons. The burden of somatic point mutations in the mtDNA control region is increased in PD brain samples [35], although it is not known whether it is accompanied by compromised mtDNA replication and transcription, similarly to what has been shown for AD brains [155]. Other studies reported insignificantly higher levels of somatic point mutations in the frontal cortex and *substantia nigra* of PD patients, in the *ND4* gene of complex I [156], and in the *ND5* gene in muscle biopsies, in comparison to healthy controls [157]. This trend has not been replicated in all studies [158]. Also mtDNA deletions seem to play a role in PD pathogenesis [34, 159]. *Substantia nigra* has the highest frequency of mtDNA deletions among all tissues, possibly due to the prooxidative dopamine metabolism mentioned earlier [34]. They reach a very high level (up to 50%) in PD patients and in healthy elderly subjects, which correlates with decreased cytochrome c activity, although the deletion level is only slightly higher in PD patients than in age-matched controls [34]. However, in patients with early stage PD and those with incidental Lewy body disease (ILBD) the burden of somatic mutations in SN neurons is significantly higher than in a control group [160].

5. POLYMORPHISMS IN NUCLEAR GENES INVOLVED IN MITOCHONDRIAL FUNCTIONING AND BIOGENESIS AFFECT PD RISK

Mitochondrial biogenesis is coordinated by three PGC-1 family proteins, peroxisome proliferator-activated receptor gamma coactivator 1-alpha (PGC-1alpha) [161], PGC-1beta and PGC-1-related coactivator (PRC) [162]. PGC-1alpha integrates the activity of a wide range of transcription factors responsible for mitochondrial biogenesis [163]. All PGC-1 family members are able to co-activate nuclear respiratory factors (NRF1, NRF2) and trans-activate NRFs-responsive genes directly and indirectly involved in mitochondrial biogenesis. The NRFs regulate the majority of nuclear genes encoding subunits of five respiratory complexes [162]. They also act on genes whose products conduct mtDNA transcription and replication (TFAM; mitochondrial transcription factor B1, TFB1M; mitochondrial transcription factor B2, TFB2M; mitochondrial RNA polymerase, POLRMT; mitochondrial DNA polymerase gamma, POLG1; RNA component of mitochondrial RNA processing endoribonuclease, RMRP) and those encoding components of the mitochondrial translation apparatus (ribosomal proteins, tRNA synthetases), mitochondrial protein import and assembly machinery (translocases of the outer mitochondrial membrane, TOM20, TOM70), and heme biosynthesis enzymes [153, 164], see also (Fig. **2**).

There is a growing body of evidence that nucleus – encoded proteins participating at different stages in mitochondrial maintenance and biogenesis are important for PD pathogenesis.

5.1. Nucleus-encoded Respiratory Chain Subunits

Polymorphisms/mutations in nuclear genes encoding respiratory chain subunits seem obvious candidates for PD risk factors. However, according to the PDgene most of the obtained results, so far, are negative [24]. Only a single such gene has been implicated in PD pathogenesis that codes for a subunit of mitochondrial complex I - NADH dehydrogenase (ubiquinone) flavoprotein 2 (NDUFV2). Homozygotes with a substitution Ala29Val in the mitochondrial targeting sequence have a 2.4-fold higher PD risk than a control group [165]. A screen of the entire *NDUFV2* coding region in 33 familial and 238 sporadic PD patients of North African Arab-Berber ethnicity revealed two cases of a novel substitution p.K209R (c.626A>G), possibly with an autosomal dominant mode of inheritance [166], (Fig. **2**).

5.2. PGC-1alpha

Of the PGC-1 family members only *PGC-1alpha* polymorphisms have been analyzed in the context of PD risk in a single study [167]. Interactions with a coding mtDNA SNP 10398G present in haplogroups J, K and I were found, however, only in subgroups comprising less than 200 patients [167]. The rs6821591 C/C genotype was associated with the risk of early onset PD, with age of PD onset, and with longevity (Fig. **2**). The rs2970848 G/G allele was associated with the risk of late onset PD ($p = 0.027$). The *PGC-1alpha* rs8192678 (c.1444C>T, Gly482Ser) C/C genotype was associated with longevity ($p = 0.019$), but not with PD risk [167]. Functional studies demonstrated that c.1444C>T decreased

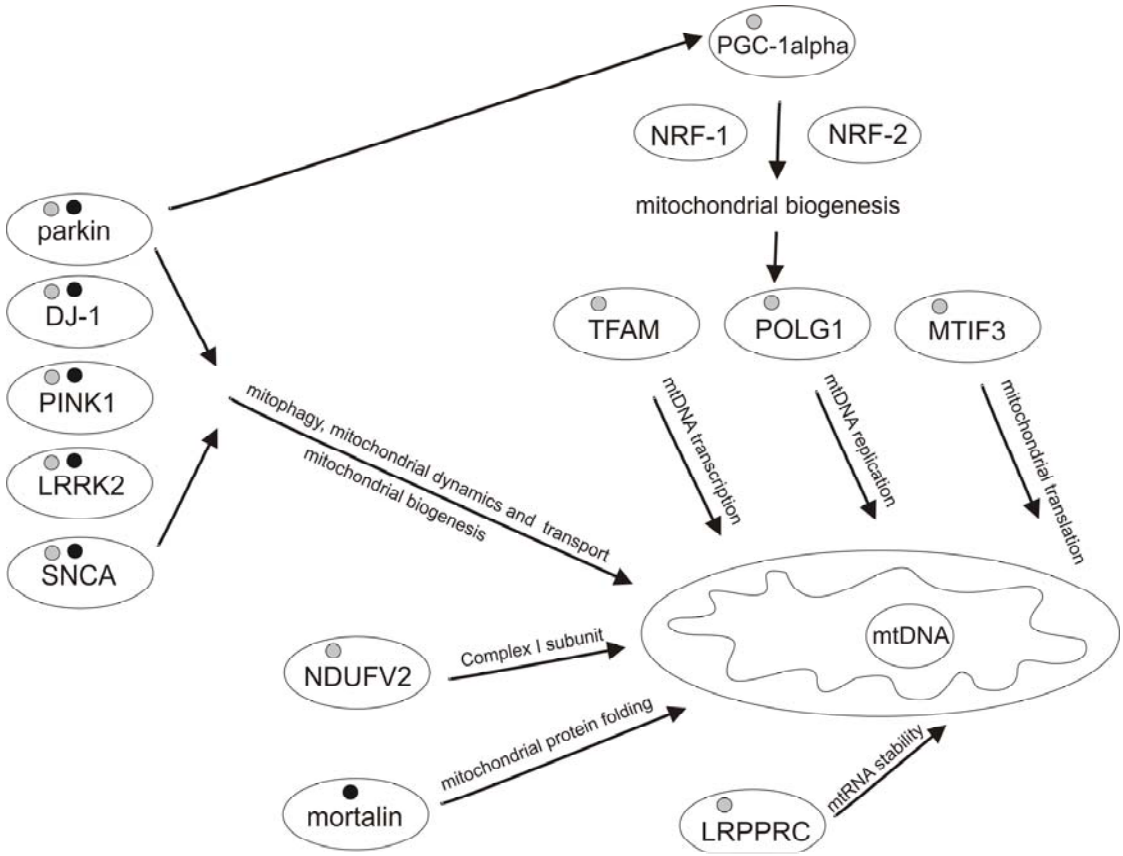

Fig. (2). Genes related to mitochondrial function and implicated in PD pathogenesis.

About 10% of PD cases arise due to mutations in *PARK* genes. *PARK2* (parkin), *PARK6* (PINK1), and *PARK7* (DJ-1), are responsible for autosomal recessive PD forms, while *PARK1* (α-SNCA) and *PARK8* (LRRK2) mutations cause autosomal dominant PD. The influence of polymorphisms in *PARK* genes on PD risk has been extensively studied. Recent research have demonstrated that variation in other (than *PARK)* mitochondria-related genes may modulate PD risk. Parkin, PINK1, DJ-1, LRRK2 and α-SNCA are involved in regulation of mitochondrial function to different extent. Parkin regulates PGC-1alpha levels through PARIS. PGC-1alpha coordinates mitochondrial biogenesis through trans-activation of NRF1/2-responsive genes, such as *NDUFV2*, *TFAM*, *POLG1*, *MTIF3*. The function given above arrows is general. Black dots designate mutations. Grey dots designate polymorphisms.

the PGC-1alpha level [168] and that this variant of the protein co-activated downstream transcription factors less efficiently [169]. *In silico* analysis suggested that splicing of the T-allele could be defective [170]. Interestingly, the c.1444C >T allele was associated previously with type II diabetes [171] and hypertension [172], while carriers of at least one c.1444C>T allele had an almost two times higher risk of late onset AD (LOAD) than those with the C/C genotype, however, only among APOE4 carriers [102].

A meta-analysis of genome-wide expression studies has shown that *PGC-1alpha* and its target genes involved in cellular bioenergetics are downregulated in sporadic PD patients in comparison with control groups [173]. Also in parkin deficiency conditions the PGC-1alpha level is changed [174, 175], reviewed in [14]. Thus, PGC-1alpha has been proposed as a therapeutic target for PD treatment. However, there are some important concerns that should be stressed. It has recently been shown that sustained overexpression of PGC-1alpha in the rat nigrostriatal system leads to metabolic alterations followed by degeneration of DA neurons. This result indicates that maintaining physiological levels of therapeutic proteins is critical [176]. Moreover, the functional redundancy among the PGC-1 coactivator family members should be taken into account, as well, for review see [162].

5.3. Other Genes Involved in Mitochondrial Biogenesis: *HSPA9*, *LRPPRC* and *TOMM40*

Apart from the PGC-1 family co-activators, several other proteins involved in mitochondrial biogenesis have been implicated in PD pathogenesis, such as mortalin and LRPPRC.

Mortalin is a mitochondrial matrix chaperone of the heat shock protein 70 family encoded by the *HSPA9* gene. Its levels are downregulated in PD brains, animal and cellular PD models [177-180] and correlate with disease progression in PD patients [179]. So far, four potentially pathogenic variants in the mortalin gene have been identified in PD patients from Spain (two missense R126W, P509S; one intron 8 insertion of 17 bp, predicted to affect RNA splicing) and Germany (A476T) but not in control groups [181, 182], Fig. **2**.

The Translocase of Outer Mitochondrial Membrane 40 homolog (TOMM40) is essential for import of proteins into

mitochondria [183]. Previously, a common polymorphic, deoxythymidine-tract in intron 6 of the *TOMM40* gene (rs10524523) has been associated with Alzheimer's disease [184, 185]. However, we have found no association between this polymorphism and the risk of PD [186].

The LRPPRC protein (leucine rich PPR-motif containing protein, also known as LRP130) is one of the seven proteins of the pentatricopeptide repeat (PPR) family that all localize to mitochondria [187]. It plays a role in the post-transcriptional regulation of all mtDNA-encoded mRNAs, increasing their stability [188, 189]. Sequencing of the *LRPPRC* gene in 46 atypical EOPD patients has revealed over 20 variants, some of potential significance for PD [190], (Fig. **2**).

Above-mentioned data suggest that association studies of *PGC-1 family, NRFs*, *LRPPRC*, *HSPA9* and other genes involved in the regulation of mitochondrial biogenesis ought to be performed.

5.4. Genes Encoding mtDNA Expression Machinery

Mitochondrial transcription factors A and two B isoforms (TFAM and TFB1M, TFB2M, respectively) and mitochondrial RNA polymerase (POLRMT) form the basal mtDNA transcription apparatus [187]. TFB1M and TFB2M are recruited to the transcription initiation complex through the TFAM's C-terminal tail. TFAM is also implicated in packaging of mtDNA in a nucleoid-like structure, displaying both mtDNA promoter-specific and non sequence-specific mtDNA binding capacity [191, 192]. The use of TFAM in experimental PD therapy has been suggested since it protects from oxidative stress and improves mitochondrial respiratory functions in cellular and animal models [193, 194]. A molecular therapy based on transfection of either free or mtDNA-complexed recombinant TFAM led to a marked improvement of mitochondrial functioning in cybrids with mtDNA from PD patients, characterized by decreased mtDNA and mtRNA levels and impaired respiratory capacity [144]. Eleven weeks after single recombinant TFAM-mtDNA complex application, the mtDNA and mtRNA levels were restored, and the levels of PGC1alpha mRNA, TFAM and ETC proteins increased, indicative of an induction of mitochondrial biogenesis and also a feedback loop between TFAM and/or mtDNA levels and PGC1alpha. Control cybrids, as well as those exhibiting limited mitochondrial dysfunction, did not respond to the therapy, which suggested selectivity of the treatment without interference with normal mitochondrial functioning.

TFB1M and, to a lesser extent, TFB2M display also a 12S rRNA methyltransferase activity and thus contribute to the biogenesis of mitochondrial ribosomes and translation [187, 195]. This suggests that mitochondrial transcription and translation are regulated in a coordinated manner. TFB2M is more potent in promoting mtDNA transcription than TFB1M, while the latter one is primarily a 12S rRNA methyltransferase; reviewed in [187].

Mutational screening of *TFAM*, *TFB1M* and *TFB2M* has not revealed any potentially pathogenic mutations in PD patients [196, 197]. No *TFB1M* or *TFB2M* polymorphisms showed association with PD risk [197]. In the case of *TFAM*, only our previous study reported that the rs2306604 G/G genotype is an independent risk factor for PD (OR 1.789, 95% CI 1.162-2.755, p=0.008) [198], (Fig. **1**). Other studies, including GWAS and a meta-analysis, have not found any association with PD risk [24, 196, 199-201]. Our data indicated that four of five haplotypes containing allele G had higher frequencies in the PD group, but without reaching statistical significance [198]. Earlier *in silico* analysis showed that the *TFAM* rs2306604G (IVS4 + 113 G) allele creates a putative new splice donor and a cryptic splice acceptor resulting in a truncated TFAM protein of 102 amino acids [202], although its presence is yet to be demonstrated *in vivo*.

As to the translation machinery, a polymorphism in one of the two mitochondrial translation initiation factors that operate in mammalian mitochondria - translation initiation factor 3 (MTIF3) - was recently associated with PD risk [203-205]. The protein is crucial for ribosome assembly and initiation of translation in mitochondria; reviewed in [187]. The rs7669 c.798C>T polymorphism of the *MTIF3* gene showed allelic or genotype association with PD [203-205]. The rs7669 T/T-genotype is associated with a decreased *MTIF3* mRNA expression in comparison to the C/C-genotype [205], (Fig. **2**). A dearth of MTIF3 could impair the ability of mitochondria to respond rapidly and dynamically to stress or damage by limiting the pool of available mtDNA-encoded proteins, and thus the organelle biogenesis. An increased PD risk could be a consequence.

5.5. Genes Encoding mtDNA Replication Machinery

Defects of the mtDNA replication machinery (mutations in the DNA polymerase gamma 1, *POLG1* and *Twinkle* genes) have been found to contribute to the parkinsonian phenotype [206-210].

Twinkle is a DNA helicase unwinding mtDNA at the replication fork, essential for mtDNA maintenance and copy number regulation in mammals [211, 212]. As previously mentioned, targeted overexpression of mutant twinkle in SN DA neurons recapitulated some of the cardinal features of Parkinson disease [66]. However, the role of twinkle variants in idiopathic PD remains to be addressed.

The *POLG1* gene coding for the catalytic subunit of the heterotrimeric mitochondrial DNA polymerase is responsible for mtDNA replication (5'→3' polymerase activity) and repair (3'→5' exonuclease activity) in mammals [213, 214]. POLG1 contains at its N-terminus a variable poly-glutamine tract (poly-Q) encoded by exon 2 CAG repeat sequence crucial for the exonuclease activity and the proofreading of mtDNA. The most common STR variant has ten CAG repeats (10Q, frequency >80%), a moderately common allele 11Q has a frequency of 6-12%, while minor variants 6Q-9Q and 12Q-14Q each have frequencies not exceeding 4%. Rare poly-Q variants of *POLG1* have been shown to increase sporadic PD risk in Finnish [215], North American Caucasians (non-10Q) [216], Swedish (non-10/11Q) [217], and Norwegian populations (non-10/11Q) [218], though it was not confirmed in all studies [219]. A recent meta-analysis of association studies corroborated the notion that rare non-10Q variants are significantly associated with PD risk (p=0.0017) [218], (Fig. **2**). A bioinformatic analysis showed aberrant

mRNA folding energy for non-10/11Q variants [217]. A recombinant POLG1 lacking the poly-glutamine tract (delta10Qs) overexpressed in a cellular model exhibited increased mRNA, protein level and polymerase activity in comparison with a control variant (10Qs) [220]. Those cells had a lower than normal mtDNA content. However, no changes in the composition, amount or assembly state of respiratory chain complexes and no up-regulation of TFAM or mtSSB expression have been found [220].

These results indicate that rare *POLG1* STR variants could modulate the POLG1 functioning, but more detailed functional studies are necessary to elucidate the underlying molecular mechanism.

5.6. Interplay Between Nuclear and Mitochondrial Genomes in PD Pathogenesis – Old Actors on New Stage

As mentioned earlier, proper mitochondrial activity requires a well-coordinated expression of mitochondrial and nuclear genomes.

We hypothesized that the impact of nuclear genes on PD risk could be modified by the mtDNA background (see also Fig. **1**). Parkin has been shown to interact with TFAM and mtDNA *in vitro* and *in vivo* and to increase mtDNA transcription, replication and mitochondrial mass in a cellular model [18, 19]. Those results suggested that parkin and TFAM could operate in the same physiological pathway, prompting us to analyze the interaction between mitochondrial haplogroups/clusters and 1) *PARK2* polymorphisms, and 2) *TFAM* variation. Our results indicated that genotypes G/G V380L of *PARK2* and G/G rs2306604 of *TFAM* increased PD risk in combination with the prooxidative background of the most common mitochondrial HV cluster although the rs2306604 *TFAM* has been shown to be an independent PD risk factor [198, 221]. We have also found a significant interaction between the rs2306604 G/G genotype of *TFAM* and the V380L G/G genotype of *PARK2*, in subjects with the mitochondrial HV cluster. Those findings imply that simultaneous presence of G/G V380L *PARK2* and G/G rs2306604 *TFAM* in the pro-oxidative HV cluster background is a PD risk factor with detrimental influence stronger than predicted by additive model [221], (Fig. **1**).

Meta-analyses of *PARK2* polymorphism studies indicate that allele C of V380L is protective against PD, but only when all ethnicities and studies with control groups violating Hardy-Weinberg equilibrium are included [24]. Earlier reports showed either no association for V380L or pointed to the G/G V380L genotype as increasing the PD risk and/or allel C decreasing it [222, 223]. Among PD patients potentially exposed to pesticides (postulated to increase PD risk) those carrying allele C of V380L had a higher age at onset [224]. Interestingly, this allele also decreases the risk of familial and sporadic progressive supranuclear palsy (PSP), a tauopathy that genetically, clinically and histopathologically partially overlaps PD [25]. The amino acid position 380 of parkin is located in the IBR (in between RING) domain. Structural analyses indicate that the domain is likely responsible for stabilizing the geometry and relative orientation of the two RING domains of parkin [24]. Thus, the V380L replacement could bring about a decreased interaction with E2 protein–ubiquitin conjugating enzymes and impaired ubiquitination of substrates [24].

A plethora of polymorphisms in other nuclear genes including *PARK* genes have been implicated in PD pathogenesis (Fig. **1**). The results are available in the database for PD genetic association studies and feature also meta-analyses [24]. It can be speculated that the influence of nuclear genes (especially those tightly regulating mitochondrial functioning) could be modified by mtDNA background. Recent findings have demonstrated that the levels of inflammatory biomarkers related to air-pollution, such as interleukin-6 (IL-6) and tumor necrosis factor-alpha (TNF-alpha), are higher in subjects with mitochondrial haplogroup H (as compared to subjects with haplogroup U) [225] (Fig. **1**), however, common genetic variation in *IL-6* or *TNF-alpha* genes has not been associated with late-onset sporadic Parkinson's disease.

6. CONCLUSION

Individual susceptibility to PD is a result of complex interactions between genetic factors, environment and physiological aging. Natural consequence of such complexity is the pathophysiological heterogeneity of PD. It seems plausible that different molecular pathways are compromised to a different extent in individual PD patients, possibly creating "molecular/genetic" subtypes of the disease. To date, mitochondrial dysfunction and/or increased oxidative stress are only found in a subset of sporadic PD patients (30%) [226]. Detailed understanding of this obvious heterogeneity is of great importance for the development of future individualized therapies, for example those targeting mitochondrial dysfunction and/or oxidative stress [9].

Although there is convincing evidence of mitochondrial dysfunction both in sporadic and familial PD cases, none of the genes discussed here (*NDUFV2*, *PGC-1alpha*, *HSPA9*, *LRPPRC*, *MTIF3*, *POLG1*, *TFAM*), have been highlighted in PD genome-wide association studies (GWAS). To date, *PARK1* and *PARK8* common variation (coding for SNCA and LRRK2, respectively), and *TAU* are fairly consistently reported in GWAS as risk factors for PD [24, 200, 227-236]. This can be partially due to the specificity of GWAS, which usually do not allow for the detection of rare variants or markers with small effects that are lost in the background noise.

The presented results of candidate-gene driven association studies and sequence analyses in case and control groups underscore the differences in the predisposition to develop PD related to common variation of nuclear and mitochondrial genomes. There is growing evidence from functional studies that common variants of mtDNA influence numerous biological parameters, such as ATP and oxidative stress levels, mtDNA transcription/replication rate, and nuclear gene expression pattern. The interactions between the two genomes in PD pathogenesis can be addressed through carefully designed association studies. The main challenge for the future is to secure sufficient statistical power allowing for reliable conclusions to be drawn (several thousands of participants). Ideally, the environmental PD risk factors should also be taken into account, such as caffeine intake, smoking or exposure to mitochondrial toxins, because they may constitute important confounding factors, leading to discrepant results of association studies [237]. It would be also important to verify whether clinical subtypes of PD

(such as the previously mentioned tremor-prevalent and PIGD forms) are associated with different molecular mechanisms or different genetic background, a question not addressed so far in association studies.

An integrative approach combining detailed characterization of mitochondrial parameters (bioenergetics, ROS levels, biogenesis, mitophagy, mitochondrial dynamics) along with other highly related pathways (such as response to oxidative stress, cellular clearance pathways, etc.) in PD patients and healthy controls with well defined genetic background (mtDNA haplogroups, nuclear gene variants tightly regulating mitochondrial functioning and oxidative stress such as *PGC1alpha, TFAM, POLG1, PARK2*, *HSPA9*, etc.) would greatly advance the understanding of the impact of common genetic variants on PD risk. It remains to be established whether knowing of individual patient's genotype could help to select them for a specific type of therapy, e.g. mitochondria-targeted one, or help to predict the response to treatment. The usefulness of genetic markers (such as individual *PARK2* mutations) is already being tested along with clinical symptoms considered as predisposing to PD in so called enriched risk cohorts approach, reviewed by [238].

CONFLICT OF INTEREST

The author(s) confirm that this article content has no conflicts of interest.

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