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

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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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Keywords: Association studies, Mitochondrial dysfunction, mtDNA haplogroups, Nuclear genes, Parkinson’s disease, Polymorphism.

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 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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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.

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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 MITOCOンドRIAL 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 Ca²⁺ overload driven by unique to substantia nigra voltage-dependent L-type Ca²⁺ 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 H₂O₂ 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 Ca²⁺ overload [34].

3. MITOCOンドRIAL DYSFUNCTION IN PD PATHOGENESIS

Mitochondria are crucial in energy generation, ROS production, Ca²⁺ 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-
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 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).

In addition, haplogroup J has been associated with longevity [103-106]. It has also been shown to protect from osteoarthritis, 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 [112, 113]. 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 (VO2max) 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
Indeed, functional studies have demonstrated that compromised OXPHOS as occurs in sepsis and stroke [122,123] has been shown to exert a protective effect in temporarily maintaining ATP and ROS production. 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 VO2max 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 H2O2-induced oxidative stress than F1a, D4a, or N9a cybrids [135]. A N9a cybrid had a higher oxygen consumption and H2O2-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 mitochondrial DNA 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 haplogroup 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 haplogroup 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 pro-oxidative 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 MITOCOCHONDRIAL 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 1 - 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
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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 indicate 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], thought 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 allele 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
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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REFERENCES

[1] Samil, A.; Nutt, J.G.; Ransom, B.R. Parkinson's disease. Lancet, 2004, 363, 1783-1793.
[2] Fearnley, J.M.; Lees, A.J. Ageing and Parkinson's disease: substantia nigra regional selectivity. Brain, 1991, 114 (Pt 5), 2283-2301.
[3] van Nuenen, B.F.; van Eimeren, T.; van der Vegt, J.P.; Buhmann, C.; Klein, C.; Bloem, B.R.; Siebner, H.R. Mapping preclinical compensation in Parkinson's disease: an imaging genomics approach. Mov. Disord., 2009, 24 Suppl 2, S703-710.
[4] Braak, H.; Del Tredici, K.; Rub, U.; de Vos, R.A.; Jansen Steur, E.N.; Braak, E. Staging of brain pathology related to sporadic Parkinson's disease. Neurobiol. Aging, 2003, 24, 197-211.
[5] Hawkes, C.H. The prodromal phase of sporadic Parkinson's disease: does it exist and if so how long is it? Mov. Disord., 2008, 23, 1799-1809.
[6] Jankovic, J. Parkinson's disease: clinical features and diagnosis. J. Neurol. Neurosurg. Psychiatry., 2008, 79, 368-376.
[7] Langston, J.W. The Parkinson's complex: parkinsonism is just the tip of the iceberg. Ann. Neurol., 2006, 59, 591-596.
[8] Selikhova, M.; Williams, D.R.; Kempster, P.A.; Holton, J.L.; Revesz, T.; Lees, A.J. A clinicopathological study of subtypes in Parkinson's disease: Brain, 2009, 132, 2947-2957.
[9] Obeso, J.A.; Rodriguez-Oroz, M.C.; Goetz, C.G.; Marin, C.; Kordower, J.H.; Rodriguez, M.; Hirsch, E.C.; Farrer, M.; Schapira, A.H.; Halliday, G. Missing pieces in the Parkinson's disease puzzle. Nat. Med., 2010, 16, 653-661.
[10] Elbaz, A.; Bower, J.H.; Maraganore, D.M.; McDonnell, S.K.; Peterson, B.J.; Ahlskog, J.E.; Schaid, D.J.; Rocca, W.A. Risk tables for parkinsonism and Parkinson's disease. J. Clin. Epidemiol., 2002, 55, 25-31.
[11] Abou-Sleiman, P.M.; Muqit, M.M.; Wood, N.W. Expanding insights of mitochondrial dysfunction in Parkinson's disease. Nat. Rev. Neurosci., 2006, 7, 207-219.
[12] Exner, N.; Lutz, A.K.; Haass, C.; Winklhofer, K.F. Mitochondrial dysfunction in Parkinson's disease: molecular mechanisms and pathophysiological consequences. EMBO. J., 2012, 31, 3038-3062.
[13] Plöls, A.; Winklhofer, K.F. Parkin, PINK1 and mitochondrial integrity: emerging concepts of mitochondrial dysfunction in Parkinson's disease. Acta. Neuropathol., 2012, 123, 173-188.
[14] Gaweł-Wałerych, K.; Zekanowski, C. Integrated pathways of parkin control over mitochondrial maintenance - relevance to Parkinson's disease pathogenesis. Acta. Neurobiol. Exp. (Wars), 2013, 73, 199-224.
[15] Sai, Y.; Zou, Z.; Peng, K.; Dong, Z. The Parkinson's disease-related genes act in mitochondrial homeostasis. Neurosci. Biobehav. Rev., 2011, 36, 2034-2043.
[16] Thomas, K.J.; McCoy, M.K.; Blackinton, J.; Beilina, A.; van der Brug, M.; Sandebring, A.; Miller, D.; Marcie, D.; Cedazo-Minguez, A.; Cookson, M.R. DJ-1 acts in parallel to the PINK1/parkin pathway to control mitochondrial function and autophagy. Hum. Mol. Genet., 2011, 20, 40-50.
[17] Joselin, A.P.; Hewitt, S.J.; Callaghan, S.M.; Kim, R.H.; Chung, Y.H.; Mak, T.W.; Shen, J.; Slack, R.S.; Park, D.S. ROS-dependent regulation of Parkin and DJ-1 localization during oxidative stress in neurons. Hum. Mol. Genet., 2012, 21, 4888-4903.
[18] Kuroda, Y.; Mitsu, T.; Kunishige, M.; Shono, M.; Akaike, M.; Azuma, H.; Matsumoto, T. Parkin enhances mitochondrial biogenesis in proliferating cells. Hum. Mol. Genet., 2006, 15, 883-895.
[19] Rothfuss, O.; Fischer, H.; Hasegawa, T.; Maisel, M.; Leitner, P.; Miesel, F.; Sharma, M.; Bornemann, A.; Berg, D.; Gasser, T.; Patenge, N. Parkin protects mitochondrial genome integrity and supports mitochondrial DNA repair. Hum. Mol. Genet., 2009, 18, 3832-3850.
[20] Rideout, H.J.; Stefani, L. The Neurobiology of LRRK2 and its Role in the Pathogenesis of Parkinson's Disease. Neurochem. Res., 2013.
[21] Mullin, S.; Schapira, A. Alpha-synuclein and mitochondrial dysfunction in Parkinson's disease. Mol. Neurobiol., 2013, 47, 587-597.
[22] Calvo, S.E.; Mootha, V.K. The mitochondrial proteome and human disease. Annu. Rev. Genomics. Hum. Genet., 2010, 11, 25-44.
[23] Meisinger, C.; Sickmann, A.; Pfanner, N. The mitochondrial proteome: from inventory to function. Cell, 2008, 134, 22-24.
[24] Lill, C.M.; Roehr, J.T.; McQueen, M.B.; Kavvoura, F.K.; Bagade, S.; Schjeide, B.M.; Schjeide, L.M.; Meissner, E.; Zauft, U.; Allen, N.C.; Liu, T.; Schilling, M.; Anderson, K.J.; Beecham, G.; Berg, D.; Biernacka, J.M.; Brice, A.; DeStefano, A.L.; Do, C.B.; Eriksson, N.; Factor, S.A.; Farrer, M.J.; Foroud, T.; Gasser, T.; Hamza, T.; Hardy, J.A.; Heutink, P.; Hill-Burns, E.M.; Klein, C.; Lau-touelle, J.C.; Maraganore, D.M.; Martin, E.R.; Martinez, M.; Myers, R.H.; Nalls, M.A.; Pankratz, N.; Payami, H.; Satake, W.; Scott, W.K.; Sharma, M.; Singleton, A.B.; Stefansson, K.; Toda, T.; Tzeng, J.Y.; Young, P.; Tanzi, R.E.; Khoury, M.J.; Zipp, F.; Leahrach, H.; Ioannidis, P.J.; Bertram, L. Comprehensive research synopsis and systematic meta-analyses in Parkinson's disease genetics: The PDGene database, http://www.pdgene.org/, PLoS. Genet., 2012, 8, e1002548.
[25] Warner, T.T.; Schapira, A.H. Genetic and environmental factors in the cause of Parkinson's disease. Ann Neurol, 2003, 53 Suppl 3, S16-23; discussion S23-15.
[26] Fujioka, S.; Wszolek, Z.K. Update on genetics of parkinsonism. Neurodegener. Dis., 2012, 10, 257-260.
[27] Braak, H.; Del Tredici, K. Poor and protracted myelination as a contributory factor to neurodegenerative disorders. Neurobiol. Aging., 2004, 25, 19-23.
[28] Chang, C.Y.; Lee, H.; Song, T.K.; Yang, A.Y.; Kim, J.; Liu, L.; Isacson, O. Cell type-specific gene expression of midbrain dopaminergic neurons reveals molecules involved in their vulnerability and protection. Hum. Mol. Genet., 2005, 14, 1709-1725.
[29] Greene, J.G.; Dinglestone, R.; Greenamyer, J.T. Gene expression profiling of rat midbrain dopamine neurons: implications for selective vulnerability in parkinsonism. Neurobiol. Dis., 2005, 18, 19-31.
[30] Grimm, J.; Mueller, A.; Hefli, F.; Rosenthal, A. Molecular basis for catecholaminergic neuron diversity. Proc. Natl. Acad. Sci. U S A., 2004, 101, 13891-13896.
[31] Chan, C.S.; Guzman, J.N.; Ilie, I.; Mercer, J.N.; Rick, C.; Tkatch, T.; Meredith, G.E.; Sarmiento, D.J. 'Rejuvenation' protects neurons in mouse models of Parkinson's disease. Nature, 2007, 447, 1081-
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Betarbet, R.; Sherer, T.B.; Greenamyre, J.T. Animal models of Parkinson's disease. Bioessays, 2002, 24, 308-318.

Shemer, T.B.; Betarbet, R.; Stout, A.K.; Lund, S.; Baptista, M.; Panov, A.V.; Cookson, M.R.; Greenamyre, J.T. An in vitro model of Parkinson's disease: linking mitochondrial impairment to altered alpha-synuclein metabolism and oxidative damage. J. Neurosci., 2002, 22, 7006-7015.

Betarbet, R.; Canet-Aviles, R.M.; Sherer, T.B.; Mastroberardino, P.G.; McLendon, C.; Kim, J.H.; Lund, S.; Na, H.M.; Taylor, G.; Bence, N.F.; Kopito, R.; Seo, B.B.; Yagi, T.; Yagi, A.; Klinefelter, G.; Cookson, M.R.; Greenamyre, J.T. Intersecting pathways to neurodegeneration in Parkinson's disease: Effects of the pesticide rotenone on DJ-1, alpha-synuclein, and the ubiquitin-proteasome system. Neurobiol. Dis., 2006, 22(2), 404-20.

Soffner, J.M.; Brown, M.D.; Torroni, A.; Lott, M.T.; Cabell, M.F.; Mirra, S.S.; Beal, M.F.; Yang, C.C.; Gearing, M.; Salvo, R.; et al. Mitochondrial DNA variants observed in Alzheimer disease and Parkinson disease patients. Genomics, 1993, 17, 171-184.

Surh, Y.J.; Kim, H.J. Neurotrophic effects of tetradydrobiopterin and underlying mechanisms. Exp. Neurobiol., 2010, 19, 63-70.

Landrigan, P.J.; Sonawane, B.; Butler, R.N.; Trasande, L.; Callan, R.; Droller, D. Early environmental origins of neurodegenerative disease in later life. Environ. Health. Perspect., 2005, 113, 1230-1233.

Krug, S.E.; Watt, W.C.; Marcinek, D.J.; Kapur, R.P.; Schenkman, K.A.; Palmer, R.D. Mice with mitochondrial complex I deficiency develop a fatal encephalomyopathy. Cell. Metab., 2008, 7, 312-320.

Qutnata, A.; Kruse, S.E.; Kapur, R.P.; Sanz, E.; Palmer, R.D. Complex I deficiency due to loss of Ndufs4 in the brain results in progressive encephalopathy resembling Leigh syndrome. Proc. Natl. Acad. Sci. U S A, 2010, 107, 10996-11001.

Leong, D.W.; Komen, J.C.; Hewitt, C.A.; Arnaud, E.; McKenzie, M.; Phipson, B.; Bahlo, M.; Laskowski, A.; Kinkel, S.A.; Davey, G.M.; Heath, W.R.; Voss, A.K.; Zahedi, R.P.; Pitt, J.J.; Chrast, R.; Sickmann, A.; Ryan, M.T.; Smyth, G.K.; Thorburn, D.R.; Scott, H.S. Proteomic and metabolomic analyses of mitochondrial complex I-deficient mouse models reveal spontaneous B2 short interspersed nuclear element (SINE) insertion into NDAD dehydrogenase (ubiquinone) Fe-S protein 4 (Ndufs4) gene. J. Biol. Chem., 2012, 287, 20652-20663.

Sterky, F.H.; Hoffman, A.F.; Milenkovic, D.; Bao, B.; Paganelli, A.; Edgar, D.; Wilom, B.; Lupino, C.R.; Olson, L.; Larsson, N.G. Altered dopamine metabolism and increased vulnerability to MPTP in mice with partial deficiency of mitochondrial complex I in dopamine neurons. Hum. Mol. Genet., 2012, 21, 1078-1089.

Galter, D.; Perondi; K.; Yoshitake, T.; Lindqvist, E.; Hoffer, B.; Kehr, J.; Larsson, N.G.; Olson, L. MitoPark mice mirror the slow progression of key symptoms and L-DOPA response in Parkinson's disease. Genes Brain Behav., 2010, 9, 173-181.

Ekstrand, M.I.; Terzioglu, M.; Galter, D.; Zhu, S.; Hofstetter, C.; Lindqvist, E.; Thams, S.; Bergstrand, A.; Hansson, F.S.; Trifunovic, A.; Hoffer, B.; Culmell, S.; Mohammed, A.H.; Olson, L.; Larsson, N.G. Progressive parkinsonism in mice with respiratory-chain-deficient dopamine neurons. Proc. Natl. Acad. Sci. U S A, 2007, 104, 1325-1330.

Sterky, F.H.; Lee, S.; Wilom, B.; Olson, L.; Larsson, N.G. Impaired mitochondrial transport and Parkin-independent degeneration of respiratory chain-deficient dopamine neurons in vivo. Proc. Natl. Acad. Sci. U S A, 2011, 108, 12937-12942.

Pickrell, A.M.; Pinto, M.; Hida, A.; Moraes, C.T. Striatal dysfunctions associated with mitochondrial DNA damage in dopaminergic neurons in a mouse model of Parkinson's disease. J. Neurosci., 2011, 31, 17649-17658.

Song, L.; Shan, Y.; Lloyd, K.C.; Cortopassi, G.A. Mutant Twinkle increases dopaminergic neurodegeneration, mtDNA deletions and modulates Parkin expression. Hum. Mol. Genet., 2012, 21(23), 5147-5157.

Gavruruso, M.A.; Willems, P.; van den Brand, M.; Valsecchi, F.; Kruse, S.; Palmier, R.; Smetink, J.; Nijtmans, L. Mitochondrial complex III stabilizes complex I in the absence of NDUF54 to provide partial activity. Hum. Mol. Genet., 2012, 21, 115-120.

Wallace, D.C.; Brown, M.D.; Lott, M.T. Mitochondrial DNA variation in human evolution and disease. Gene, 1999, 238, 211-230.

Finnila, S.; Lehtonen, M.S.; Majamaa, K. Phylogenetic network for...
European mtDNA. *Am. J. Hum. Genet.*, 2001, 68, 1475-1484.

Herrnstadt, C.; Elson, J.L.; Fayh, E.; Preston, G.; Turnbull, D.M.; Anderson, C.; Ghosh, S.S.; Olefsky, J.M.; Beal, M.F.; Davis, R.E.; Howell, N. Reduced-mediated-network analysis of complete mitochondrial DNA coding-region sequences for the major African, Asian, and European haplogroups. *Am. J. Hum. Genet.*, 2002, 70, 1152-1171.

Torrioni, A.; Huoponken, K.; Francalacci, P.; Petrozzi, M.; Morelli, L.; Scozzari, R.; Obini, D.; Savontaus, M.L.; Wallace, D.C. Classification of European mtDNAs from an analysis of three European populations. *Genetics*, 1996, 144, 1835-1850.

Torrioni, A.; Richards, M.; Macaulay, V.; Forster, P.; Villems, R.; Norby, S.; Savontaus, M.L.; Huoponken, K.; Scozzari, R.; Bandelt, H.J. mtDNA haplogroups and frequency patterns in Europe. *Am. J. Hum. Genet.*, 2000, 66, 1173-1177.

Gomez-Duran, A.; Pacheu-Grau, D.; Lopez-Gallardo, E.; Diez-Sanchez, C.; Montoya, J.; Lopez-Perez, M.J.; Ruiz-Pesini, E. Unmasking the causes of multifactorial disorders: OXPHOS differences in Parkinson disease. *Hum. Mol. Genet.*, 2010, 19, 3343-3353.

Kong, Q.P.; Yao, Y.G.; Sun, C.; Bandelt, H.J.; Zhu, C.L.; Zhang, Y.P. Phylogeny of east Asian mitochondrial DNA lineages inferred from complete sequences. *Am. J. Hum. Genet.*, 2003, 73, 671-676.

Nieminen, A.K.; Molanen, J.S.; Tanaka, M.; Hervonen, A.; Hurme, M.; Lehtimaki, T.; Arii, Y.; Hirose, N.; Majamaja, K. A combination of three common inherited mitochondrial DNA polymorphisms promotes longevity in Finnish and Japanese subjects. *Eur. J. Hum. Genet.*, 2005, 13, 166-170.

Silva, W.A., Jr.; Bonatto, S.L.; Holanda, A.J.; Ribeiro-Dos-Santos, A.K.; Paixao, B.M.; Goldman, G.H.; Abc-Sanches, K.; Rodriguez-Delfin, L.; Barbosa, M.; Paco-Larson, M.L.; Petzl-Erler, M.L.; Vante, V.; Santos, S.E.; Zago, M.A. Mitochondrial genome diversity of Native Americans supports a single early entry of founder populations into America. *Am. J. Hum. Genet.*, 2002, 71, 187-192.

Tanaka, M.; Takeyasu, T.; Fuku, N.; Li-Jun, G.; Kurata, M. Mitochondrial genome single nucleotide polymorphisms and their phylogenies in the Japanese. *Am. J. Hum. Genet.*, 2004, 71, 729-740.

Swerdlov, R.H.; Parks, J.K.; Davis, J.N., 2nd; Cassarino, D.S.; Trimmer, P.A.; Currie, L.J.; Dougherty, J.; Bridges, W.S.; Bennett, J.P., Jr.; Wooten, G.F.; Parker, W.D., Jr. Maternal inheritance in Parkinson’s disease. *Ann. Neurol.*, 2007, 61, 1835-1850.

Burn, D.J.; Chinnery, P.F. Mitochondrial DNA haplogroup cluster UKJ1 reduces the risk of PD. *Ann. Neurol.*, 2005, 57, 564-567.

Ghezzi, D.; Marelli, C.; Achilli, A.; Goldwurm, S.; Pizzolli, G.; Barone, P.; Pellecchia, M.T.; Stanzione, P.; Brusa, L.; Bentivoglio, A.; Bonuccelli, U.; Petrozzi, L.; Abbruzzese, G.; Marchese, R.; Corelli, P.; Grimaldi, D.; Martinelli, P.; Ferrarese, C.; Garavaglia, B.; Sangiorgi, S.; Carelli, V.; Torroni, A.; Albanese, A.; Zeviani, M. Mitochondrial DNA haplogroup K is associated with a lower risk of Parkinson's disease in Italians. *Eur. J. Hum. Genet.*, 2005, 13, 748-752.

Kusnudinova, E.; Gilyazova, I.; Ruiz-Pesini, E.; Derbeneva, O.; Khusainova, R.; Khiydiyatova, I.; Magzhanov, R.; Wallace, D.C. A mitochondrial etiology of neurodegenerative diseases: evidence from Parkinson's disease. *Ann. N. Y. Acad. Sci.*, 2008, 1147, 1-20.

Mehta, P.; Mellick, G.D.; Rowe, D.B.; Halliday, G.M.; Jones, M.M.; Manwaring, N.; Vandeboma, H.; Silburn, P.A.; Wang, J.J.; Mitchell, P.; Sue, C.M. Mitochondrial DNA haplogroups J and K are not protective for Parkinson's disease in the Australian community. *Mov. Disord.*, 2009, 24, 290-292.

Latsoudis, H.; Spanaki, C.; Chlouverakis, G.; Pliatikas, A. Mitochondrial DNA polymorphisms and haplogroups in Parkinson's disease and control individuals with a similar genetic background. *J. Hum. Genet.*, 2008, 53, 349-356.

Gaweda-Walerzyc, K.; Maruszak, A.; Safranow, K.; Bialecka, M.; Kłodowska-Duda, G.; Czyzewski, K.; Slawek, J.; Rudzinska, M.; Styczynska, M.; Opala, G.; Drodzick, M.; Canter, J.A.; Barcikowska, M.; Zekanowski, C. Mitochondrial DNA with subhaplogroups are associated with Parkinson's disease in a Polish PD cohort. *J. Neural. Transm.*, 2008, 115, 1521-1526.

Ruiz-Pesini, E.; Lapena, A.C.; Diez-Sanchez, C.; Perez-Martos, A.; Montoya, J.; Alvarez, E.; Diaz, M.; Urries, A.; Montoro, L.; Lopez-Perez, M.J.; Enriguez, J.A. Human mtDNA haplogroups associated with high or reduced spermatozoa motility. *Am. J. Hum. Genet.*, 2007, 80, 682-696.

Ruiz-Pesini, E.; Mishmar, D.; Brandon, M.; Procaccio, V.; Wallace, D.C. Effects of purifying and adaptive selection on regional variation in human mtDNA. *Science*, 2004, 303, 223-226.

Wallace, D.C. The mitochondrial genome in human evolution: the road to therapeutics and performance enhancement. *Font. Biochem.*, 2007, 13, 169-180.

Montiel-Sosa, F.; Ruiz-Pesini, E.; Enriguez, J.A.; Marcellou, A.; Montoya, J.; Alvarez, E.; Diaz, M.; Urries, A.; Montoro, L.; Lopez-Perez, M.J.; et al. Differences of sperm motility in mitochondrial DNA haplogroup U sublineages. *Gene*, 2006, 368, 21-27.

Sun, C.; Kong, Q.P.; Zhang, Y.P. The role of climate in human mitochondrial DNA evolution: a reappraisal. *Genomics*, 2007, 89, 334-342.

Amo, T.; Brand, M.D. Were inefficient mitochondrial haplogroups selected during migrations of modern humans? A test using modular kinetic analysis of coupling in mitochondria from cybrid cell lines. *Biochem. J.*, 2007, 404, 345-351.

Elson, J.L.; Turnbull, D.M.; Taylor, R.W. Testing the adaptive selection of human mtDNA haplogroups: an experimental bioenergetics approach. *Biochem. J.*, 2007, 404, e3-5.

Kivisild, T.; Shen, P.; Wall, D.P.; Do, B.; Sung, R.; Davis, K.; Passarino, G.; Underhill, P.A.; Scharfe, C.; Tonroni, A.; Scozzari, R.; Modiano, D.; Coppa, A.; de Knijff, P.; Feldman, M.; Cavalli-Sforza, L.L.; Oefner, P.J. The role of selection in the evolution of human mitochondrial genome. *Science*, 2006, 311, 377-387.

Maruszak, A.; Safranow, K.; Branicki, W.; Gaweda-Walerzyc, K.; Polsiech, E.; Gabryelewicz, T.; Canter, J.A.; Barcikowska, M.; Zekanowski, C. The impact of mitochondrial and nuclear DNA variants on late-onset Alzheimer's disease risk. *J. Alzheimers. Dis.*, 2011, 27, 197-210.
Mitochondrial and Nuclear Genetic Polymorphisms Related to PD Risk

Current Genomics, 2013, Vol. 14, No. 8 555

with longevity in a Finnish population. *Hum. Genet.*, 2003, 112, 29-33.

[104] Domínguez-Garrido, E.; Martínez-Redondo, D.; Martín-Ruiz, C.; Gomez-Durán, A.; Ruiz-Pesini, E.; Madero, P.; Tamparillas, M.; Montoya, J.; von Zglinicki, T.; Diez-Sanchez, C.; Lopez-Perez, M.J. Association of mitochondrial haplogroup J and mtDNA oxidative damage in two different North Spain elderly populations. *Biol. Genet.*, 2009, 10, 435-442.

[105] De Benedistis, G.; Rose, G.; Carrieri, G.; De Luca, M.; Falcone, E.; Passarino, G.; Bonafe, M.; Monti, D.; Baggio, G.; Bertolini, S.; Mari, D.; Mattace, R.; Franceschi, C. Mitochondrial DNA inherited variants are associated with successful aging and longevity in humans. *Faseb J.*, 1999, 13, 1532-1536.

[106] Ross, O.A.; McCormack, R.; Curran, M.D.; Duguid, R.A.; Barnett, Y.A.; Rea, I.M.; Middleton, D. Mitochondrial DNA polymorphism: its role in longevity of the Irish population. *Exp. Gerontol.*, 2001, 36, 1161-1178.

[107] Rego-Perez, I.; Fernandez-Moreno, M.; Fernandez-Lopez, C.; Arenas, J.; Blanco, F.J. Mitochondrial DNA haplogroups: role in the prevalence and severity of knee osteoarthritis. *Arthritis Rheum.*, 2008, 58, 2387-2396.

[108] Rego, I.; Fernandez-Moreno, M.; Fernandez-Lopez, C.; Gomez-Reino, J.J.; Gonzalez, A.; Arenas, J.; Blanco, F.J. Role of European mitochondrial DNA haplogroups in the prevalence of hip osteoarthritis in Galicia, Northern Spain. *Ann. Rheum. Dis.*, 2010, 69, 210-213.

[109] Marcello, A.; Martínez-Redondo, D.; Dahmani, Y.; Casajas, J.A.; Ruiz-Pesini, E.; Montoya, J.; Lopez-Perez, M.J.; Diez-Sanchez, C. Human mitochondrial variants influence on oxygen consumption. *Mitochondrion*, 2009, 9(1), 27-30.

[110] Martínez-Redondo, D.; Marcello, A.; Casajas, J.A.; Ara, I.; Dahmani, Y.; Montoya, J.; Ruiz-Pesini, E.; Lopez-Perez, M.J.; Diez-Sanchez, C. Human mitochondrial haplogroup H: the highest VO2max consumer--is it a paradox? *Mitochondrion*, 2010, 10, 102-107.

[111] Fernandez-Moreno, M.; Tamayo, M.; Soto-Hermida, A.; Mosquera, A.; Oreiro, N.; Fernandez-Lopez, C.; Fernandez, J.L.; Rego-Perez, I.; Blanco, F.J. mtDNA haplogroup J Modulates telomere length and Nitric Oxide production. *BMC Musculoskelet. Disord.*, 2011, 12, 283.

[112] Bellizzi, D.; D'Aquila, P.; Giordano, M.; Montesanto, A.; Passarino, G. Global DNA methylation levels are modulated by mitochondrial DNA variants. *Epigenomics*, 2012, 4, 17-27.

[113] Kenney, M.C.; Chwa, M.; Atlano, S.R.; Pavlis, J.M.; Falatoonzadeh, P.; Ramirez, C.; Malik, D.; Hsu, T.; Goo, S.; Soe, K.; Neeburn, A.B.; Boyer, D.S.; Kuppermann, B.D.; Jazwinski, S.M.; Gabriel, J.P.; Matos, I.; Lopes, G.; Ferro, J.M.; Viana-Baptista, M.; Simoes, R.M.; Pinto, A.N.; Inoue, A.; Goswami, A.; Viana-Baptista, M.; Correia, M.; Wang, H.; Gao, X.; McGrath, M.; Deer, D.; De Vivo, I.; Arning, L.; Haghikia, A.; Taherzadeh-Fard, E.; Saft, C.; Andrich, J.; Pula, B.; Hoxtermann, S.; Wieczorek, S.; Akkad, D.A.; Perrech, M.; Gold, R.; Epplen, J.T.; Chan, A. Mitochondrial haplogroup H correlates with ATP levels and age at onset in Huntington disease. *J. Mol. Med. (Berl)*, 2010, 88, 431-436.

[114] Baudouin, S.V.; Saunders, D.; Tiangyou, W.; Elson, J.L.; Poynter, J.; Pyle, A.; Keers, S.; Turnbull, D.M.; Howard, N.; Chinnery, P.F. Mitochondrial DNA and survival after sepsis: a prospective study. *Lancet.*, 2005, 366, 2118-2121.

[115] Rosa, A.; Fonseca, B.V.; Krug, T.; Manso, H.; Gouveia, L.; Alberio, L.; Gama, I.; Gaspar, G.; Correia, M.; Viana-Baptista, M.; Simoes, R.M.; Pinto, A.N.; Taipa, R.; Ferreira, C.; Fontes, J.R.; Silva, M.R.; Gabriel, J.P.; Matos, I.; Lopes, G.; Ferro, J.M.; Vicente, A.M.; Oliveira, S.A. Mitochondrial haplogroup H1 is protective for ischemic stroke in Portuguese patients. *BMC Med. Genet.*, 2008, 9, 57.

[116] Hudson, G.; Nalls, M.; Evans, J.R.; Breen, D.P.; Winder-Rhodes, S.; Morrison, K.E.; Morris, H.R.; Williams-Gray, C.H.; Barker, R.A.; Singleton, A.B.; Hardy, J.; Wood, N.E.; Burn, D.J.; Chinnery, P.F. Two-stage association study and meta-analysis of mitochondrial DNA variants in Parkinson disease. *Neurology*, 2013, 80, 2042-2048.

[117] Marusza, A.; Canter, J.A.; Styczynska, M.; Zekanowski, C.; Barcikowska, M. Mitochondrial haplogroup H and Alzheimer's disease--Is there a connection? *Neurobiol. Aging.*, 2008, 30(11), 1749-1755.

[118] Coto, E.; Gomez, J.; Alonso, B.; Corao, A.I.; Diaz, M.; Menendez, M.; Martinez, C.; Calatayud, M.T.; Moris, G.; Alvarez, V. Late-onset Alzheimer's disease is associated with mitochondrial DNA 7028C/haplogroup H and D310 poly-C tract heteroplasy. *Neurogenetics*, 2011, 12, 345-346.

[119] Carelli, V.; Vergani, L.; Bernazzi, B.; Zampieron, C.; Buchi, L.; Valentino, M.; Rengo, C.; Torroni, A.; Martinuzzi, A. Respiratory function in cybrid cell lines carrying European mtDNA haplogroups: implications for Leber's hereditary optic neuropathy. *Mech. Dis.* 2009, 78, 7-14.

[120] Amo, T.; Yadava, N.; Oh, R.; Nicholls, D.G.; Brand, M.D. Experimental assessment of bioenergetic differences caused by the common European mitochondrial DNA haplogroups H and T. *Gene.*, 2008, 411, 69-76.

[121] Muller, E.E.; Brunner, S.M.; Mayr, J.A.; Stanger, O.; Spelr, W.; Koller, B. Functional differences between mitochondrial haplogroup T and haplogroup H in HEK293 cybrid cells. PLoS One, 2012, 7, e25267.

[122] Tanaka, M.; Fukushima, T.; Nishigaki, Y.; Matsu, H.; Segawa, T.; Watanabe, S.; Kato, K.; Ito, M.; Nozawa, Y.; Yamada, Y. Women with mitochondrial haplogroup N9a are protected against metabolic syndrome. *Diabetes.*, 2007, 56, 518-521.

[123] Fuji, N.; Park, K.S.; Yamada, Y.; Ishigaki, Y.; Cho, Y.M.; Masu, T.; Segawa, T.; Watanabe, S.; Kato, K.; Ito, M.; Nozawa, Y.; Lee, H.K.; Tanaka, M. Mitochondrial haplogroup N9a confers resistance against type 2 diabetes in Asians. *Am. J. Hum. Genet.*, 2007, 80, 407-415.

[124] Takasaki, S. Mitochondrial haplogroups associated with Japanese centenarians, Alzheimer's patients, Parkinson's patients, type 2 diabetic patients and healthy non-obese young males. *J. Genet. Genomics*, 2009, 36, 425-434.

[125] Takasaki, S. Mitochondrial haplogroups associated with Japanese Alzheimer's patients. *J. Bioenerg. Biomembr.*, 2009, 41, 407-410.

[126] Hwang, S.; Kwak, S.H.; Bhat, J.; Kang, H.S.; Lee, Y.R.; Koo, B.K.; Park, K.S.; Lee, H.K.; Cho, Y.M. Gene expression pattern in transmitochondrial cytoplastomic hybrid cells harboring type 2 diabetes-associated mitochondrial DNA haplogroups. PLoS One, 2011, 6, e22116.

[127] Lin, T.K.; Lin, H.Y.; Chen, S.D.; Chuang, Y.C.; Chuang, J.H.; Wang, P.W.; Huang, S.T.; Tiao, M.M.; Chen, J.B.; Liou, C.W. The detection of cybrid cells carrying mitochondrial haplogroups in the Taiwanese population of ethnic Chinese background: an extensive in vitro tool for the study of mitochondrial genomic variations. *Oxid. Med. Cell. Longev.*, 2012, 2012, 824275.

[128] Pesce, V.; Nicassio, L.; Fracasso, F.; Micocci, C.; Cantatore, P.; Gadaleta, M.N. Acetyl-L-carnitine activates the pexisome proliferator-activated receptor-gamma coactivators PGC-1alpha/PGC-1beta-dependent signaling cascade of mitochondrial biogenesis and 14484 mutations on an mtDNA lineage. *Am. J. Hum. Genet.*, 1997, 60, 381-387.
decreases the oxidized peroxiredoxins content in old rat liver. *Rejuvenation Res.*, 2012, 15, 136-139.

[137] Lee, H.K.; Song, J.H.; Shin, C.S.; Park, D.J.; Park, K.S.; Lee, K.U.; Koh, C.S. Decreased mitochondrial DNA content in peripheral blood precedes the development of non-insulin-dependent diabetes mellitus. *Diabetes Res. Clin. Pract.*, 2012, 97, 347-351.

[138] Picca, A.; Fracasso, F.; Pesce, V.; Cantatore, P.; Joseph, A.M.; Leeuwenburgh, C.; Gadadela, M.N.; Lezza, A.M. Age- and calorie restriction-related changes in rat brain mitochondrial DNA and TFAM binding. *Age (Dordr).* 2012, 35(5), 1607-1620.

[139] Cree, L.M.; Patel, S.K.; Pyle, A.; Lynn, S.; Turnbull, D.M.; Chinney, P.F.; Walker, M. Age-related decline in mitochondrial DNA copy number in isolated human pancreatic islets. *Diabetologia*, 2008, 51, 1440-1443.

[140] Short, K.R.; Bigelow, M.L.; Kahl, J.; Singh, R.; Coenens-Schimke, J.; Raghavakaimal, S.; Nair, K.S. Decline in skeletal muscle mitochondrial function with aging in humans. *Proc. Natl. Acad. Sci. U.S.A.* 2005, 102, 5618-5623.

[141] Monikaraj, F.; Aravind, S.; Gokulakrishnan, K.; Sathishkumar, C.; Prabu, P.; Prabu, D.; Mohan, V.; Balasubramanyam, M. Accelerated aging as evidenced by increased telomere shortening and mitochondrial DNA depletion in patients with type 2 diabetes. *Mol. Cell. Biochem.*, 2012, 363, 343-350.

[142] Barrientos, A.; Casademont, J.; Cardellach, F.; Estivill, X.; Urbano-Marquez, A.; Nunez, V. Reduced steady-state levels of mitochondrial RNA and increased mitochondrial DNA amount in human brain with aging. *Brain Res. Mol. Brain. Res.*, 1997, 52, 284-289.

[143] Blokhin, A.; Vykshina, T.; Komoly, S.; Kalman, B. Variations in mitochondrial DNA copy numbers in MS brains. *J. Mol. Neurosci.*, 2008, 35, 283-287.

[144] Keeny, P.M.; Quigley, C.K.; Dunham, L.D.; Papageorge, C.M.; Iyer, S.; Thomas, R.R.; Schwarz, K.M.; Trimper, P.A.; Khan, S.M.; Portell, F.R.; Bergquist, K.E.; Bennett Jr., J.P. Mitochondrial Gene Therapy Augments Mitochondrial Physiology in a Parkinson's Disease Cell Model. *Hum. Gene. Ther.*, 2009, 20(8), 897-907.

[145] Borland, M.K.; Mohanakumar, K.P.; Rubinstein, J.D.; Keeny, P.M.; Xie, J.; Capaldi, R.; Dunham, L.D.; Trimper, P.A.; Bennett, J.P., Jr. Relationships among molecular genetic and respiratory properties of Parkinson's disease cybrid cells show similarities to Parkinson's brain tissues. *Biochim. Biophys. Acta.*, 2009, 1792, 68-74.

[146] Iwaasa, M.; Umeda, S.; Ohso, T.; Takamatsu, C.; Fukuhu, A.; Iwasaki, H.; Shinagawa, H.; Hamasaki, N.; Kang, D. 1-Methyl-4-phenylniperidinium ion, a toxin that can cause parkinsonism, alters branched structures of DNA. *J. Neurochem.*, 2002, 82, 30-37.

[147] Umeda, S.; Muta, T.; Ohso, T.; Takamatsu, C.; Hamasaki, N.; Kang, D. The D-loop structure of human mtDNA is destabilized directly by 1-methyl-4-phenylniperidinium ion (MPP+), a parkinsonism-causing toxin. *Eur. J. Biochem.*, 2000, 267, 200-206.

[148] Kraysitberg, Y.; Kudryavtseva, I.; McKee, A.C.; Geula, C.; Kowalski, S.; Smigrodzki, R.; Parks, J.; Parker, W.D. High frequency of mitochondrial DNA control-region mutations that suppress mitochondrial function with aging in humans. *Proc. Natl. Acad. Sci. U S A.*, 2004, 101, 10726-10731.

[155] Coskun, P.E.; Beal, M.F.; Wallace, D.C. Alzheimer's brains harbor somatic mtDNA control-region mutations that suppress mitochondrial transcription and replication. *Proc. Natl. Acad. Sci. U S A.*, 2004, 101, 10726-10731.

[160] Lin, M.T.; Cantuti-Castelvetri, I.; Zheng, K.; Jackson, K.E.; Tan, Y.B.; Arzberger, T.; Lees, A.J.; Betensky, R.A.; Beal, M.F.; Simon, D.K. Somatic mitochondrial DNA mutations in early Parkinson and incidental Lewy body disease. *Ann. Neurol.*, 2012, 71, 850-854.

[161] Lin, M.T.; Cantuti-Castelvetri, I.; Zheng, K.; Jackson, K.E.; Tan, Y.B.; Arzberger, T.; Lees, A.J.; Betensky, R.A.; Beal, M.F.; Simon, D.K. Somatic mitochondrial DNA mutations in early Parkinson and incidental Lewy body disease. *Ann. Neurol.*, 2012, 71, 850-854.

[162] Lin, M.T.; Cantuti-Castelvetri, I.; Zheng, K.; Jackson, K.E.; Tan, Y.B.; Arzberger, T.; Lees, A.J.; Betensky, R.A.; Beal, M.F.; Simon, D.K. Somatic mitochondrial DNA mutations in early Parkinson and incidental Lewy body disease. *Ann. Neurol.*, 2012, 71, 850-854.

[163] Lin, M.T.; Cantuti-Castelvetri, I.; Zheng, K.; Jackson, K.E.; Tan, Y.B.; Arzberger, T.; Lees, A.J.; Betensky, R.A.; Beal, M.F.; Simon, D.K. Somatic mitochondrial DNA mutations in early Parkinson and incidental Lewy body disease. *Ann. Neurol.*, 2012, 71, 850-854.

[164] Li, Z.; Song, J.; Shin, C.S.; Park, D.J.; Park, K.S.; Lee, K.U.; Koh, C.S. Decreased mitochondrial DNA content in peripheral blood precedes the development of non-insulin-dependent diabetes mellitus. *Diabetes Res. Clin. Pract.*, 2012, 97, 347-351.

[165] Lee, H.K.; Song, J.H.; Shin, C.S.; Park, D.J.; Park, K.S.; Lee, K.U.; Koh, C.S. Decreased mitochondrial DNA content in peripheral blood precedes the development of non-insulin-dependent diabetes mellitus. *Diabetes Res. Clin. Pract.*, 2012, 97, 347-351.

[166] Li, Z.; Song, J.; Shin, C.S.; Park, D.J.; Park, K.S.; Lee, K.U.; Koh, C.S. Decreased mitochondrial DNA content in peripheral blood precedes the development of non-insulin-dependent diabetes mellitus. *Diabetes Res. Clin. Pract.*, 2012, 97, 347-351.

[167] Li, Z.; Song, J.; Shin, C.S.; Park, D.J.; Park, K.S.; Lee, K.U.; Koh, C.S. Decreased mitochondrial DNA content in peripheral blood precedes the development of non-insulin-dependent diabetes mellitus. *Diabetes Res. Clin. Pract.*, 2012, 97, 347-351.
Mitochondrial and Nuclear Genetic Polymorphisms Related to PD Risk

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M.B.; Middleton, F.A.; Roche, J.C.; Scherzer, C.R. PGC-1alpha, a potential therapeutic target for early intervention in Parkinson's disease. Sci. Transl. Med., 2010, 2, 52ra73.

[174] Shin, J.H.; Ko, H.S.; Kang, H.; Lee, Y.; Lee, Y.I.; Pletinkova, O.; Troconzo, J.C.; Dawson, V.L.; Dawson, T.M. PARIS (ZN7464) repression of PGC-1alpha contributes to neurodegeneration in Parkinson's disease. Cell, 2011, 144, 689-702.

[175] Pacelli, C.; De Rosno, D.; Signorile, A.; Grattaglione, I.; di Tullio, G.; D’Orazio, A.; Nico, B.; Comi, G.P.; Ronchi, D.; Ferrarini, E.; Pinolo, D.; Sibiel, P.; Schubert, S.; Gaballo, A.; Villani, G.; Cocco, T. Mitochondrial defect and PGC-1alpha dysfunction in parkin-associated familial Parkinson’s disease. Biochim. Biophys. Acta, 2011, 1812, 1041-1053.

[176] Ciron, C.; Lengacher, S.; Dusonchet, J.; Aebischer, P.; Schneider, B.L. Sustained expression of PGC-1alpha in the rat nigrostriatal system selectively impairs dopaminergic function. Hum. Mol. Genet., 2012, 21, 1861-1876.

[177] Jin, J.; Meredith, G.E.; Chen, L.; Zhou, Y.; Xu, J.; Shi, F.S.; Lockhart, P.; Zhang, J. Quantitative proteomic analysis of mitochondrial proteins: relevance to Lewy body formation and Parkinson’s disease. Brain Res. Mol. Brain Res., 2005, 134, 119-138.

[178] Jin, J.; Hulette, C.; Wang, Y.; Zhang, T.; Pan, C.; Wadlwa, R.; Zhang, J. Proteomic identification of a stress protein, mortalin/mitochondrial transcription factor A, relevant to Parkinson’s disease. Mol. Cell. Proteomics, 2006, 5, 1193-1204.

[179] Shi, M.; Jin, J.; Wang, Y.; Beyer, R.P.; Kitsou, E.; Albin, R.L.; Gearing, M.; Pan, C.; Zhang, J. Mortalin: a protein associated with progression of Parkinson disease? J. Neuropathol. Exp. Neurol., 2008, 67, 117-124.

[180] Chiasserini, D.; Tozzi, A.; de lure, A.; Tantucce, M.; Susta, F.; Orvietani, P.L.; Koya, K.; Binaglia, L.; Calabresi, P. Mortalin inhibition in experimental Parkinson’s disease. Mov. Disord., 2011, 26, 1639-1647.

[181] Barberia, L.F.; Schelling, C.; Kato, H.; Rapaport, D.; Woitalla, D.; Burbulla, L.F.; Schelling, C.; Kato, H.; Rapaport, D.; Woitalla, D.; Upham, R.; Holm, M.; Schulte, C.; Sharma, M.; Illig, T.; Bauer, P.; Jung, S.; Nordheim, A.; Schols, L.; Riess, O.; Kruger, R. Dissecting the role of the mitochondrial chaperone mortalin in Parkinson’s disease. Neurobiol. Aging, 2009, 309-322.

[182] De Mena, L.; Coto, E.; Sanchez-Ferrer, E.; Ribacoba, R.; Guisasola, L.M.; Salvador, C.; Blazquez, M.; Alvarez, V. Mutational screening of the mortalin gene (HSPA9) in Parkinson’s disease. Neurology, 2010, 280, 1193-1198.

[183] De Mena, L.; Coto, E.; Sanchez-Ferrer, E.; Ribacoba, R.; Guisasola, L.M.; Salvador, C.; Blazquez, M.; Alvarez, V. Mutation screening of the mortalin gene (HSPA9) in Parkinson’s disease. Neurology, 2010, 11535-11543.

[184] Humphries, A.D.; Streimann, I.C.; Stojanovski, D.; Johnston, A.J.; Humphries, A.D.; Streimann, I.C.; Stojanovski, D.; Johnston, A.J.; Gearing, M.; Pan, C.; Zhang, J. Mortalin: a protein associated with mitochondrial homeostasis. J. Neurosci., 2008, 117-124.

[185] Shindo, M.; Kanki, T.; Kang, D.; Sunagawa, K.; Tsutsui, H.; Hayashi, Y.; Yoshida, M.; Yamato, M.; Ide, T.; Wu, Z.; Ochi-Shindou, M.; Kanki, T.; Kang, D.; Sunagawa, K.; Tsutsui, H.; Nakanishi, H. Reverse of age-dependent memory impairment and mitochondrial DNA damage in microglia by an overexpression of human mitochondrial transcription factor A in mice. J. Neurosci., 2006, 34, 4437-4452.

[186] Shindo, M.; Kanki, T.; Kang, D.; Sunagawa, K.; Tsutsui, H.; Hayashi, Y.; Yoshida, M.; Yamato, M.; Ide, T.; Wu, Z.; Ochi-Shindou, M.; Kanki, T.; Kang, D.; Sunagawa, K.; Tsutsui, H.; Nakanishi, H. Reverse of age-dependent memory impairment and mitochondrial DNA damage in microglia by an overexpression of human mitochondrial transcription factor A in mice. J. Neurosci., 2008, 38, 124-130.

[187] Shindo, M.; Kanki, T.; Kang, D.; Sunagawa, K.; Tsutsui, H.; Hayashi, Y.; Yoshida, M.; Yamato, M.; Ide, T.; Wu, Z.; Ochi-Shindou, M.; Kanki, T.; Kang, D.; Sunagawa, K.; Tsutsui, H.; Nakanishi, H. Reverse of age-dependent memory impairment and mitochondrial DNA damage in microglia by an overexpression of human mitochondrial transcription factor A in mice. J. Neurosci., 2009, 38, 1640-1645.

[188] Larson, N.G.; Wang, J.; Wilhelmsson, H.; Oldfors, A.; Rustin, P.; Lewandoski, M.; Barsh, G.S.; Clayton, D.A. Mitochondrial transcription factor A is necessary for mtDNA maintenance and embryogenesis in mice. Nat. Genet., 1998, 19, 231-236.

[189] Noack, H.; Bednarek, T.; Heidler, J.; Ladig, R.; Holtz, J.; Szibor, M. TFAM-dependent and independent dynamics of mtDNA levels in C2C12 myoblasts caused by redox stress. Biochim. Biophys. Acta, 2006, 1760, 141-150.

[190] Bonawitz, N.D.; Clayton, D.A.; Shadel, G.S. Initiation and beyond: multiple functions of the human mitochondrial transcription machinery. Mol. Cell, 2006, 24, 813-825.

[191] Alvarez, V.; Corao, A.I.; Sanchez-Ferrer, E.; De Mena, L.; Alonso-Montes, C.; Huerta, C.; Blazquez, M.; Ribacoba, R.; Guisasola, L.M.; Salvador, C.; Garcia-Castro, M.; Coto, E. Mitochondrial transcription factor A (TFAM) gene variant in Parkinson’s disease. Neurobiol. Aging, 2008, 29, 1308-1312.

[192] Sánchez-Ferrer E.C.; Blazquez M; Ribacoba R; Guisasola LM; Salvador C; Alvarez V. Mutational screening of the mitochondrial transcription factors B1 and B2 (TFB1M and TFB2M) in Parkinson’s disease. Parkinsonism Relat. Disord., 2009, 15, 468-470.

[193] Gaweida-Walerzyk, K.; Safranow, K.; Maruszak, A.; Bialecka, M.; Kłodowska-Duda, G.; Czyzewski, K.; Slawek, J.; Rudzinska, M.; Styczynska, M.; Opala, G.; Drozdzik, M.; Kurzawski, M.; Szczadlik, A.; Canter, J.A.; Barcikowska, M.; Zekanowski, C. Mitochondrial transcription factor A variants and the risk of Parkinson’s disease. Neurosci. Lett., 2010, 469, 24-29.

[194] Belin, A.C.; Björk, B.F.; Westerlund, M.; Galter, D.; Sydow, O.; Lind, C.; Pennold, K.; Roswall, L.; Hakansson, A.; Winblad, B.; Nordstrand, H.; Granner, J.O.; Olson, L. Association study of two genetic variants in mitochondrial transcription factor A (TFAM) in Alzheimer’s and Parkinson’s disease. Neurosci. Lett., 2007, 420, 257-262.

[195] Simon-Sanchez, J.; Schulte, C.; Bras, J.M.; Sharma, M.; Gibbs, J.R.; Berg, D.; Paisan-Ruiz, C.; Lichtner, P.; Scholz, S.W.; Herold, C.; Behrouz, B.; Vilarino-Guell, C.; Heckman, M.G.; Soto-Ortolaza, A.; Auburger, G. Mitochondrial translation initiation factor 3 gene polymorphism associated with Parkinson’s disease. J. Neurosci., 2007, 124, 187-197.

[196] Abahuni, N.; Gispert, S.; Bauer, P.; Riess, O.; Kruger, R.; Becker, T.; Auburger, G. Mitochondrial translation initiation factor 3 gene polymorphism associated with Parkinson’s disease. Neurosci. Lett., 2007, 414, 126-129.

[197] Behrouz, B.; Vilarino-Guell, C.; Heckman, M.G.; Soto-Ortolaza, A.; Ashly, J.O.; Jyengar, S.; Lynch, T.; Craig, D.; Utter, R.L.; Wzolek, Z.K.; Ross, O.A.; Farrer, M.J. Mitochondrial translation initiation factor 3 polymorphism and Parkinson’s disease. Nat. Genet., 2010, 42, 228-230.

[198] Anvret, A.; Ran, C.; Westerlund, M.; Thelander, A.C.; Sydow, O.; Lind, C.; Hakansson, A.; Nordstrand, H.; Galter, D.; Belin, A.C. Possible involvement of a mitochondrial translation initiation factor 3 variant causing decreased mtDNA levels in Parkinson’s disease.
Parkinson's Disc., 2010, 2010, 491751.

[206] Baloh, R.H.; Salavaggione, E.; Milbrandt, J.; Pestrone, A. Familial parkinsonism and ophthalmoplegia from a mutation in the mitochondrial DNA helicase twinkle. Arch Neurol., 2007, 64, 998-1000.

[207] Davidson, G.; Greene, P.; Mancuso, M.; Klos, K.J.; Abshok, J.E.; Hirano, M.; DiMauro, S. Early-onset familial parkinsonism due to POLG mutations. Ann. Neurol., 2006, 59, 859-862.

[208] Luoma, P.; Melberg, A.; Rinne, J.O.; Kaukonen, J.A.; Nupponen, N.N.; Chalmers, R.M.; Oldfors, A.; Rutakorpi, I.; Peltonen, L.; Majamaa, K.; Somer, H.; Suomalainen, A. Parkin-mutation, premature menopause, and mitochondrial DNA polymerase gamma mutations--clinical and molecular genetic study. Lancet, 2004, 364, 875-882.

[209] Hudson, G.; Schaefer, A.M.; Taylor, R.W.; Tiangyou, W.; Gibson, A.; Venables, G.; Griffiths, P.; Burn, D.J.; Turnbull, D.M.; Chinnery, P.F. Mutation of the linker region of the polynucleotide gamma 1 (POLG1) gene associated with progressive external ophthalmoplegia and Parkinsonism. Arch Neurol., 2007, 64, 553-557.

[210] Orsucci, D.; Caldarazzo Ienco, E.; Mancuso, M.; Siciliano, G. POLG1-related and other "mitochondrial Parkinsonisms": an overview. J. Mol. Neurosci., 2011, 44, 17-24.

[211] Tyynismaa, H.; Sembongi, H.; Bokori-Brown, M.; Granycome, C.; Ashley, N.; Poulton, J.; Jalanko, A.; Spellbrink, J.N.; Holt, I.J.; Suomalainen, A. Twinkle helicase is essential for mtDNA maintenance and regulates mtDNA copy number. Hum. Mol. Genet., 2004, 13, 3219-3227.

[212] Spellbrink, J.N.; Li, F.Y.; Tiranti, V.; Nikkila, K.; Yuan, Q.P.; Tariq, M.; Wannooij, S.; Garrido, N.; Comi, G.; Morandi, L.; Santoro, L.; Spelbrink, J.N.; Li, F.Y.; Tiranti, V.; Nikkila, K.; Yuan, Q.P.; Tariq, M.; Wannooij, S.; Garrido, N.; Comi, G.; Morandi, L.; Santoro, L.; Spelbrink, J.N.; Toivonen, J.M.; Hakkaart, G.A.; Kurkela, J.M.; Bartrop, R.; Das, S.K.; Davidzon, G.; Greene, P.; Mancuso, M.; Klos, K.J.; Abshok, J.E.; Hirano, M.; DiMauro, S. Early-onset familial parkinsonism due to mutations in the gene encoding Twinkle, a phage T7 gene 4-like protein localized to the human mitochondrion. Nat. Genet., 2004, 36, 223-231.

[213] Kagan, L.S. DNA polymerase gamma, the mitochondrial replisome. Annu. Rev. Biochem., 2004, 73, 293-320.

[214] Graziewicz, M.A.; Longley, M.J.; Copeland, W.C. DNA polymerase gamma function in mitochondrial DNA replication and repair. Chem. Rev., 2006, 106, 833-405.

[215] Luoma, P.T.; Eerola, J.; Ahola, S.; Hakonen, A.H.; Hellstrom, O.; Kivisto, K.T.; Tienari, P.J.; Suomalainen, A. Mitochondrial DNA polymerase gamma variants in idiopathic sporadic Parkinson disease. Neurology, 2007, 69, 1152-1159.

[216] Eerola, J.; Luoma, P.T.; Peuralinna, T.; Scholz, S.; Paison-Ruiz, C.; Suomalainen, A.; Singleton, A.B.; Tienari, P.J.; POLG1 polymorphism and parkinson's disease. Neurosci. Lett., 2010, 477, 1-5.

[217] Anvret, A.; Westerlund, M.; Sydow, O.; Willows, T.; Lind, C.; Galter, D.; Belin, A.C. Variations of the CAG trinucleotide repeat in DNA polymerase gamma (POLG1) is associated with Parkinson's disease in an Ashkenazi Jewish population. BMC Med., 2012, 11, 204.

[219] Sharma, M.; Ioannidis, J.P.; Aasly, J.O.; Amore, G.; Brice, A.; Van Broeckhoven, C.; Bertram, L.; Bozzini, M.; Crock, D.; Clarke, C.; Facheris, M.; Farrer, M.; Garraux, G.; Gispert, S.; Amin, U.; Vilarino-Guell, C.; Hadjiegiorgiou, G.M.; Hicks, A.A.; Hattori, N.; Jean, B.; Lesage, S.; Lill, C.M.; Lin, J.J.; Lynch, T.; Lichtner, P.; Lang, A.E.; Mok, V.; Jasinska-Myga, B.; Mellick, G.D.; Morrison, K.E.; Opala, G.; Pramstaller, P.P.; Pichler, I.; Park, S.S.; Quattrone, A.; Rogacheva, E.; Ross, O.A.; Stefanis, L.; Stockton, J.D.; Satake, Y.; Silbum, P.A.; Thomas, L.; Tan, E.; Tatsuta, M.; Uitti, R.J.; Witfiedel, K.; Wozulek, Z.; Xiong, B.; Yueh, K.C.; Zhao, Y.; Gasser, T.; Maragano, D.; Kruger, R. Large-scale replication and heterogeneity in Parkinson disease genetic loci. Neurology, 2012, 79, 659-667.

[220] Trotta, L.; Guella, I.; Solda, G.; Sironi, F.; Tesei, S.; Canesi, M.; Pezzoli, G.; Goldwurm, S.; Duga, S.; Asselta, R. SNCA and MAPT, but not PARK16-18, as susceptibility genes for Parkinson's disease. Neurology, 2010, 74, 2283-2286.

[221] Mata, I.F.; Yearout, D.; Alvarez, V.; Coto, E.; de Mena, L.; Riba, M.C.; Bataller, A.; Gleser, N.; Pau, E.; Cerdan, S.; Pastor, P.; Gervantes, S.; Infante, J.; Garcia-Gorostiaga, I.; Sierra, M.; Combarros, O.; Snapinn, K.W.; Edwards, K.L.; Zabetian, C.P. Replication of SNCA, MAPT and SNCA, but not PARK16-18, as susceptibility genes for Parkinson disease. Neurobiol. Aging, 2012, 33, 600-609.

[222] Ding, H.; Sarokhan, A.; Roderick, S.S.; Bakshi, R.; Maher, N.E.; Ashourian, P.; Kan, C.G.; Chang, S.; Santarlasci, A.; Swords, K.E.; Tomson, D.; Frucht, S.; Fahn, S.; Marder, K.; Clark, L.N.; Lee, J.H. Replication of SNCA as a susceptibility gene for Parkinson's disease. Neurology, 2007, 68, 659-662.

[223] Simon-Sanchez, J.; van Hilten, J.J.; van de Warrenburg, B.; Post, B.; Berkovic, S.F.; Paton, D.W.; Sillibourne, J.; Tan, E.; Tatsuta, M.; Uitti, R.J.; Witfeldel, K.; Wozulek, Z.; Xiong, B.; Yueh, K.C.; Zhao, Y.; Gasser, T.; Maragano, D.; Kruger, R. Large-scale replication and heterogeneity in Parkinson disease genetic loci. Neurology, 2012, 79, 659-667.

[224] Trotta, L.; Guella, I.; Solda, G.; Sironi, F.; Tesei, S.; Canesi, M.; Pezzoli, G.; Goldwurm, S.; Duga, S.; Asselta, R. SNCA and MAPT, but not PARK16-18, as susceptibility genes for Parkinson's disease. Neurology, 2010, 74, 2283-2286.
Mitochondrial and Nuclear Genetic Polymorphisms Related to PD Risk

Satake, W.; Nakabayashi, Y.; Mizuta, I.; Hirota, Y.; Ito, C.; Kubo, M.; Kawaguchi, T.; Tsunoda, T.; Watanabe, M.; Takeda, A.; Tomiyama, H.; Nakashima, K.; Hasegawa, K.; Obata, F.; Yoshikawa, T.; Kawakami, H.; Sakoda, S.; Yamamoto, M.; Hattori, N.; Murata, M.; Nakamura, Y.; Toda, T. Genome-wide association study identifies common variants at four loci as genetic risk factors for Parkinson's disease. *Nat. Genet.*, 2009, 41, 1303-1307.

Tsuboi, Y. Environmental-genetic interactions in the pathogenesis of Parkinson's disease. *Exp. Neurobiol.*, 2012, 21, 123-128.

Berg, D. Is pre-motor diagnosis possible?--The European experience. *Parkinsonism. Relat. Disord.*, 2012, 18 Suppl 1, S195-198.