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Review article

Parkinson's disease and mitochondrial gene variations: A review

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ABSTRACT

Parkinson's disease (PD) is a common disorder of the central nervous system in the elderly. The pathogenesis of PD is a complex process, with genetics as an important contributing factor. This factor may stem from mitochondrial gene variations and mutations as well as from nuclear gene variations and mutations. More recently, a particular role of mitochondrial dysfunction has been suggested, arising from mitochondrial DNA variations or acquired mutations in PD pathogenesis. The present review summarizes and weighs the evidence in support of mitochondrial DNA (mtDNA) variations as important contributors to the development and course of PD.

Contents

1. Introduction

Parkinson's disease (PD) is the second most common degenerative disorder of the central nervous system (CNS) surpassed only by Alzheimer's disease (AD) [1]. The incidence of PD is 8–18 per 100.000 person-years, and the prevalence is roughly 0.3% of the entire population [2]. PD affects more than 1% of people older than 60 of age and as many as 4% of those older than 80 years [2]. The etiology of PD has long been thought to include both genetics and environment [3]. As yet, there is no direct evidence to support either etiology as a causative factor. Attention to the genetic basis of PD recently resulted in different genes having been identified as contributory to PD. A single mutation may produce a heterogeneous PD phenotype [4]. It is postulated that PD not only can stem from nuclear gene variations and mutations, but that it also can result from mitochondrial gene variations and mutations. This paper reviews the evidence that mitochondrial DNA variations contribute to PD.

As the most apparent symptom, patients afflicted with PD present with tremor [5]. This typically is evident at rest, when the limb is relaxed, and disappears with voluntary movement and sleep [5]. Bradykinesia, slowness of movement, is another manifestation of PD [6], which appears as the most disabling symptom in the early stages of the disease [7], as well as rigidity, which is resistance to limb movements [5]. Postural instability [8], leading to impaired balance, festinating gait [9], and facial motion [5] are less common characteristics of the disease. In

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addition to the limitation of movement, patients afflicted with PD may suffer from mild to severe neuropsychiatric disturbances, including disorders of speech and swallowing [10], mood [11], sleep [12], cognition [13], behavior and thought [5]. The motor symptoms of PD stem from an imbalance of two neurotransmitters, dopamine and acetylcholine [14] due to the loss of dopaminergic cells in the ventral part of the pars compacta of the substantia nigra (SN) [15]. The cause of cell loss in PD is unresolved, but several mechanisms by which neurons can degenerate have been investigated [16] including the intraneuronal accumulation of the alpha-synuclein (SNCA) protein [17]. The aggregation of this protein creates inclusions in the neurons known as Lewy bodies [15,18]. Proteosomal and lysosomal system dysfunction and reduced mitochondrial activity are also signs of the disease [16]. PD is usually diagnosed by medical history and neurological examination [5]. Neuroimaging sometimes is used to identify PD, but no single laboratory test yields an accurate diagnosis of the disease. PD progresses through the five stages defined by the Hoehn and Yahr scale [19] and as rated by the Movement Disorder Society's Unified Parkinson's Disease Rating Scale (MDS-UPDRS) used in PD diagnosis [20]. PD is an incurable disease, but Levodopa (L-DOPA) therapy raises the life expectancy [21]. L-DOPA is converted into dopamine in the dopaminergic and other neurons containing enzyme Aromatic Amino Acid Decarboxylase (AAAD), also known as DOPA decarboxylase (DDC). Drugs that improve the symptoms generally raise dopamine, block dopamine breakdown, or mimic dopamine action. Of these, L-DOPA is administered with a peripheral DDC inhibitor to elevate dopamine in the brain of PD patients [22]. Dopamine agonists mimic dopamine action [23], and MAO-B inhibitors block dopamine breakdown [24]. Among drugs that exert an anti-Parkinsonian effect by raising dopamine, modafinil also lowers oxidative stress [25]. Active treatment can modulate neuronal activity and the hemodynamic response in basal ganglia of patients with PD [26] and motor symptoms of PD can be improved by bilateral high-frequency electrical stimulation of the subthalamic nucleus (STN) [27]. PD is known as idiopathic Parkinson disease when no known cause is evident. The pathogenesis of PD is a complex process; but recently, it has been attributed also to genetic factors [3]. Approximately 15% of patients with PD have a first-degree relative suffering from PD [7] and susceptibility to PD increases in first-degree relatives of both sporadic and familial cases [28] with increased risk of PD in parents and siblings of patients [29]. Evidently, PD is transmitted in some families as an autosomal dominant [4], or autosomal recessive [30] disorder, and 5% of patients with PD has a mutation of one of several specific nuclear genes [31] including α-synuclein (SNCA), PARKIN, PTEN-induced putative kinase 1 (Pink1), DJ1 or leucine-rich repeat kinase 2 gene (LRRK2), and HTR2A [32,33]. Mutations in the LRRK2 [34] and SNCA [35]result in autosomal dominant PD, while the proteins implicated in autosomal recessive PD include PARKIN [36], PINK1 [37], DJ-1 [38] and ATP13A2 [39].

1.1. Mitochondrial DNA (mtDNA) and oxidative phosphorylation (OXPHOS)

The mitochondria are cytoplasmic organelles involved in OXPHOS and adenosine triphosphate (ATP) production. MtDNA includes multiple copies of a circular structure of 16,569 base pairs [40] that are active in the synthesis of mitochondrial ribonucleic acids (RNAs) and proteins. The mitochondrial genome, depicted in Fig. 1, contains 37 intronless genes, which encode 13 subunits of the electron-transfer chain, 2 ribosomal RNA, and 22 transfer RNA [41] and is inherited exclusively from the mother [42]. The respiratory chain in the mitochondria is composed of 5 protein complexes, and of the 46 subunits of complex I, 7 proteins (ND1, ND2, ND3, ND4, ND4l, ND5, and ND6) are encoded by mtDNA, while all 4 subunits of complex II are produced by nuclear genes. Cytochrome b is the only protein of the 3 subunits of complex III that is expressed by mtDNA. Of the 13 subunits of complex IV, three proteins (COX I, COX II and COX III) are encoded by mtDNA and of the 16 subunits of complex V, two proteins (A6 and A8) are encoded by mtDNA.

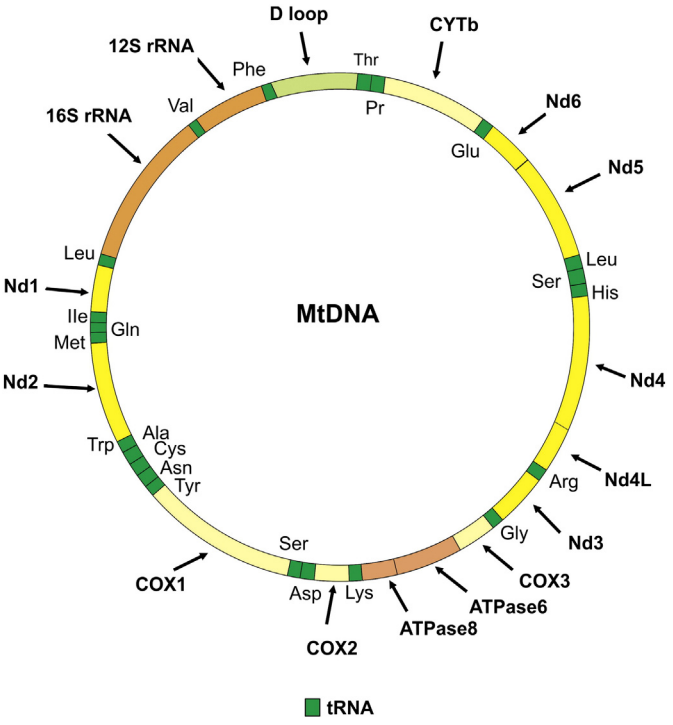

Fig. 1. Human mitochondrial genes. MtDNA (mitochondrial DNA); rRNA (ribosomal RNA); Nd (NADH Dehydrogenase); COX (cytochrome oxidase); CYTb (cytochrome b).

Of these genes, those of complex I genes are said to be the most vulnerable parts of mtDNA [43].

The mitochondria function as cellular energy factories [44]. Their dysfunction leads to failure of ATP synthesis and impaired calcium buffering [45] and they are the most important intracellular source of reactive oxygen species (ROS) [46]. Superoxide radical and its reactive metabolites, that is, ROS, are formed by approximately 2% of oxygen in and around the mitochondria [47]. On one hand, increased ROS generation damages cell membranes and raises the rate of mtDNA mutations, on the other, mtDNA mutations in turn lead to energy failure, oxidative damage, ROS generation, and aging [48]. The mutations cause mitochondrial dysfunction, and the impairment of mitochondrial respiration and OXPHOS further augments the oxidative stress, resulting in mtDNA rearrangements and deletions [49]. Compared to other organs, the brain is susceptible to oxidative damage because of its high rate of peroxidation of unsaturated fatty acids, the high levels of oxygen consumption, and the relative scarcity of antioxidant enzymes [50]. The mitochondria are critical regulators of cell death, a key feature of neurodegeneration [51], and ROS damage is a key element of many neurodegenerative disorders [52], especially PD [53,54] and AD [51,55]. The mtDNA is highly vulnerable to oxidative damage and mutation by virtue of its lack of histones, insufficient repair processes [48], and the availability of ROS from increased electron leak of the electron transport chain [56]. While somatic mtDNA mutations contribute to neurodegeneration [51], mtDNA variations give rise to more subtle damage to OXPHOS activity and hence to generation of free radicals [48].

1.2. Nuclear gene variations and mutations in PD

The mitochondria as cellular organelles are unique in animal cells as carriers of individual genomes that use transcription factors to interact with the nuclear genome [57] with nuclear gene variations and mutations reported to be associated with PD. Edwards et al. [58] performed a genome-wide association study (GWAS) and confirmed that single nucleotide polymorphisms (SNPs) in SNCA can be common risk factors for PD, as the SNPs in SNCA were associated with susceptibility to PD

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