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Peculiarities of some candidate gene polymorphisms in Parkinson's disease

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ABSTRACT
Parkinson's disease (PD) is the second most prevalent neurodegenerative disorder among elderly individuals, after Alzheimer's disease. This complex disorder manifests with multiple motor and non-motor features and is often diagnosed only after the onset of significant pathological symptoms. Based on the presumption that epigenetic mechanisms are involved in neurodevelopment and synaptic transmission, it is hypothesized that epigenetic alterations are closely connected to the development of PD. Several studies have reported that genetic risk factors are involved in PD susceptibilities. These factors play a prominent role in the predisposition and development of PD and may be closely linked to different metabolic pathways. In this review, we revise associations between single nucleotide polymorphisms (SNPs) and PD pathogenesis.
Keywords: Parkinson's disease; single nucleotide polymorphism; SNCA; GBA; VDR.

INTRODUCTION

Parkinson's disease (PD) is the second most prevalent neurodegenerative disorder among elderly individuals, after Alzheimer's disease. Manifesting with motor and non-motor features, PD is a complex disorder that is often diagnosed only after significant pathological characteristics have been revealed. It is well established that several etiological factors contribute to the development of PD – environmental factors [1, 2], genetics [3, 4], and epigenetic alterations [5], including genomic alterations. Altered epigenetic mechanisms impact the levels of certain proteins, thereby changing cellular processes and resulting in noticeable phenotypic changes [6]. Additionally, it is suggested that epigenetic mechanisms involve different processes in neurodevelopment and synaptic transmission [7]; based on this, it is presumed that epigenetic alterations are closely connected with the development of PD [8].

Parkinson's disease development is mainly caused by environmental and genetic factors [9], and their complex interactions [1, 10]. Several studies have reported that genetic risk factors significantly influence susceptibility to PD, although opinions vary with regard to their contribution to the pathogenesis of PD. At the same time, it should be noted that different populations have some peculiarities related to genetic variants that have formed over a long period of evolution.

In this paper, we aim to explore the primary gene polymorphisms and their association with PD pathogenesis to gain a better understanding of the molecular and genetic peculiarities of PD. Investigating the polymorphism of the significant causative genes is also relevant and valuable for PD therapeutic and drug investigations. Furthermore, it is crucial to identify alleles and genotypes which could play a prominent role in the early diagnosis of this disease. Ascertaining the sensible genotypes and alleles associated with the elevated susceptibility to PD could provide insights into the role of genetic risk factors for this disease at early stages.

Mayeux et al. identified that PD is predominantly distributed in the elderly population and more prevalent in men and whites compared to women and non-whites. Additionally, dementia in patients with PD is strongly correlated to the age at the onset of the motor manifestations [11]. The majority of cases of PD are sporadic and only about 10% of patients have a positive family history of PD [9].

It should be noted that causative genetic factors for parkinsonism may be closely linked to various metabolic pathways. The precise mechanisms of these pathways are unknown, but it is suggested that several ongoing mutations lead to alterations in the ubiquitin-proteasome pathway. It is presumed that PD may also be caused by alterations in the mitochondrial genome. In general, the alteration of gene expression that changes epigenetic mechanisms increases the susceptibility to PD [12]. Genome-wide association studies have revealed that PD is strongly connected to numerous genetic alterations [13]. Accumulated evidence has highlighted that genetic risk factors may have a prominent role in PD development but the main causative factors remain obscure.

SNCA (PARK1–4) GENE POLYMORPHISM AND PARKINSON'S DISEASE

The cell culture research shows an association between the *PARK2* and *PARK8* products, namely parkin (E3 ubiquitin ligase), and *LRRK2* (a kinase). Mutation in *PARK2* is a causative factor for PD and alteration in parkin's activity is associated with both inherited and sporadic PD via the RING2 parkin domain [14].

The *SNCA* gene, located on the long arm of chromosome 4 (4q21.3-22), makes a significant contribution to the pathogenesis of PD. *SNCA* has 6 exons encoding about 140 amino acid cytosolic residues. Its product, α-synuclein, contains 3 domains: the amino-terminal region (amino acids 7–87) consists of 7 imperfect repeats, each 11 amino acids in length, and is partially overlapping with the central hydrophobic domain (amino acids 61–95); the third domain is the acidic, negatively charged carboxy-terminal domain (amino acids 96–140). Maraganore et al. showed that length variability of the *SNCA REP1* allele is associated with th elevated risk of PD [3].

It should be noted that the *SNCA* gene has been identified as the first gene for autosomal-dominant PD. Moreover, *SNCA* mutation carriers tend to have early-onset PD [15]. Different missense *SNCA* mutations have been mentioned, including duplications and triplications [12], which suggests that *SNCA* mutations may be connected to the development of PD [16] and that gene duplication or triplication of the *SNCA locus* may contribute to the development of PD in an autosomal dominant form [17, 18].

Mutation in the *SNCA* gene tends to significantly increase the risk of developing PD. Therefore, it is essential to examine the genetic characteristics of this locus. Additionally, α-synuclein is involved in numerous pathologic hallmarks in PD. Research has shown that changes in the expression of this gene are associated with an elevated risk of PD. McCarthy et al. suggested that genetic regulation of *SNCA* gene splicing has a prominent role in PD progression and development [19]. It is worth noting that numerous single nucleotide polymorphisms (SNPs) in the *SNCA locus* have high susceptibility and positively correlate with PD in various populations [20].

Kay et al. have suggested that genetic variations in *SNCA* are involved in PD development [21]. Krüger et al. identified an association between common genetic variability in *SNCA* and PD development. Based on the same research, a polymorphism in the *a-SYN* gene (NACP-Rep1) promoter region, and closely linked DNA markers *D4S1647* and *D4S1628* revealed significant differences in allelic distributions between PD patients and the control group. Additionally, they noted that *ApoE* ε4 allele polymorphism of the apolipoprotein E gene was more prevalent within early-onset patients with PD than in late-onset PD [22].

The investigation of the *SNCA* gene polymorphism in the Japanese population revealed that SNPs rs356220 and rs2736990 were significantly associated with a higher risk of sporadic PD [23].

It is well known that α-synuclein, representing the critical protein in Lewy bodies, is the most important biomarker for PD. Numerous investigations show that mutations and genetic changes are closely connected and are the main factor for familiar PD development [24]. Atik et al. reported that studying different biomarkers and α-synuclein is required for accurate diagnostics [25]. Majbour et al. developed a new ELISA assay and revealed that the level of α-synuclein in cerebrospinal fluid is associated with motor symptoms of PD [26].

The study in the Chinese population showed that the *LRRK2* Gly2385Arg variant is a risk factor for the development of sporadic PD [27]. Based on a meta-analysis the following SNPs: rs181489, rs356186, rs356219, rs894278, rs2583988, rs2619364, rs10005233, and rs11931074 were found to increase the risk of PD [28]. It has been reported that polymorphism of rs3756063 may contribute to susceptibility to PD [29]. Zheng et al. revealed that carriers of rs11931074 GG and GT genotypes had an increased risk of PD [30]. Also, according to the same authors, rs11931074 gene polymorphism is closely connected to PD risk.

Thus, several findings support the opinion that genetic variability of *SNCA* is connected to PD predisposition.

GLUCOCEREBROSIDASE GENE POLYMORPHISM AND PARKINSON'S DISEASE

The human glucocerebrosidase gene (*GBA*) is located on chromosome 1q21. It is well known that this gene encodes the lysosomal enzyme glucocerebrosidase (GCase), which catalyzes the cleavage of the β-glycosidic bond of glucosylceramide into glucose and ceramide, playing a crucial role in the degradation processes of sphingolipids during glycolipid metabolism [31].

Mutations in the *GBA* gene, which result in deficient lysosomal enzyme activity in Gaucher's disease (GD), are important and common risk factors for PD and other related disorders. Gaucher's disease is an autosomal recessive (AR) inborn metabolic disorder characterized by the toxic accumulation of glucocerebroside lipids in numerous organs. The mutations in the *GBA1* gene lead to a deficiency in glucocerebrosidase activity in GD. It should be noted that *GBA* mutations are prevalent in populations with PD. Numerous studies suggest that carriers of *GBA* mutation have a higher risk of developing PD compared to the control group. It is well known that homozygous mutations in the *GBA* gene contribute to the development of GD [32]. However, the mechanism of *GBA* mutations in PD development is currently unclear. Presumably, *GBA* mutations contribute to the reduction in glucocerebrosidase enzymatic activity. Therefore, 'severe' mutations in *GBA* have a stronger association and predisposition towards PD, compared to 'milder' mutations [33].

According to literature, monogenic PD forms are associated with autosomal (therefore, dominant or recessive) inheritance patterns. Hence, they are linked to specific regions on autosomes. Gaucher's disease is characterized by the pathological accumulation of glucosylceramide within lysosomes in numerous cell types, including macrophages and neurons. *GBA* mutations are found in the majority of PD patients. This suggests that both homozygous and heterozygous *GBA* mutations are associated with the same risk of developing PD [34, 35].

Lewy bodies (α-synuclein rich neuronal protein aggregates) represent the pathological hallmark of PD. This suggests that alteration in the autophagy-lysosomal pathway may be involved in the abnormal accumulation of α-synuclein [36]. It should be noted that alterations in the following genes: *GBA*, α-synuclein (*SNCA*), and leucine-rich repeat kinase 2 (*LRRK2*), collectively represent significant genetic risk factors for the development of sporadic PD [37].

Mutations in *GBA* are associated with alterations in GCase activity and are a major cause of PD. Glucosylceramide accumulation in lysosomes may be linked to lysosomal dysfunction in the case of homozygous *GBA* mutations. Gegg et al. demonstrated no evidence of glucosylceramide accumulation in PD patients with heterozygous *GBA* mutations [38]. The *GBA* gene, which encodes a lysosomal enzyme β-glucocerebrosidase, is essential in glycolipid metabolism. Investigations have shown that carriers of *GBA* mutations among patients with PD before the age of 50 years, had some clinical symptoms at earlier ages compared to patients without mutations in this gene [33]. Homozygous mutations in the *GBA* gene cause GD, a lysosomal storage disorder. This suggests that glucocerebrosidase activity is low in patients with sporadic PD. Based on genotyping of 57 samples with PD from the brain bank, *GBA* mutations were identified in 10% of cases [39]. The L444P and N370S mutations in *GBA* increase the risk of PD [40]. It should be noted that *GBA* mutation carriers have an increased tendency and predisposition for PD development [40]. Toft et al. analyzed the *GBA* mutations (L444P and N370S) in Norwegian PD cases (2.3%, 7/311) and controls (1.7%, 8/474). These results suggest that the mentioned alleles are associated with a low risk of PD development within the Norwegian population [41]. Also, it is suggested that SNPs, especially the E326K variant, are associated with PD development [42].

Ran and Belin suggested that the N370S and L444P mutations are involved in PD pathology in Sweden's population, although the exact mechanism remains unknown. Presumably, α-synuclein accumulation may be associated with the impairment of the lysosome and autophagy pathways. They also revealed that the L444P mutation is most prevalent in northern Sweden. The E326K variant also showed an association with PD development [37], although further investigations and genetic analyses are required to make conclusive determinations. Consequently, *GBA* may be regarded as posing new challenges and providing insights into the pathophysiology of PD. It may also hold potential for early diagnosis and therapeutic strategies. Davis et al. revealed that *GBA* mutations are associated with heterogeneity in symptom progression observed in PD [43]. *GBA* mutations / SNPs may also contribute to the development of GD [44].

It is known that both homozygous and heterozygous *GBA* mutations are predominantly associated with classical parkinsonism [45, 46]. Notably, relatives of patients with GD who carry heterozygous *GBA* mutations may develop PD [47]. A genome-wide association study on *GBA* variants has suggested that the glucocerebrosidase *locus* may serve as a risk factor for PD, confirming the presence of SNPs in the gene [13, 48]. Aharon-Peretz et al., focusing on the Ashkenazi population, identified 1 or 2 mutant *GBA* alleles: among them, 23 patients were heterozygous for N370S, 4 were heterozygous for 84GG, 3 were homozygous for N370S, and 1 was heterozygous for R496H. This suggests that heterozygosity for *GBA* mutation may predispose individuals in the Ashkenazi population to PD [49].

VITAMIN D RECEPTOR GENE POLYMORPHISM AND PARKINSON'S DISEASE

The *VDR* gene (located on chromosome 12q12) is present in different tissues of our body, including the brain. It acts as a mediator for vitamin D biological functions and plays a crucial role in numerous physiological processes. As high expression of vitamin D is found in the brain [50], a decrease in vitamin D levels may be significant in the pathogenesis of PD [51]. Knekt et al. suggest that high vitamin D levels have a protective function against PD development [52].

Numerous reports have been published about the *VDR* gene polymorphism and its association with PD [51, 52, 53]. It should be noted that *VDR* plays an essential role in various neural mechanisms and is presumed to contribute to several pathways. Several relevant studies suggest that vitamin D and *VDR* may be involved in the different molecular mechanisms related to PD susceptibility [52]. It has been reported that decreased levels of vitamin D may have a prominent role in the development of PD [54]. Genetic variants of *VDR* have a prominent role in age-at-onset PD and may contribute to the predisposition and development of this disease [55].

It has been reported that *VDR* polymorphism may be involved in the susceptibility and pathogenesis of PD [56, 57], but the contributing molecular and genetic mechanisms for this association have not yet been defined and, in most cases, remain controversial [58, 59]. In addition, there are notable differences in the frequency of *VDR* polymorphism among different populations [56].

Some *VDR* polymorphisms (including BsmI, FokI, ApaI, and TaqI) are associated with PD in the Korean population [60]. In addition, a genotyping study on the Chinese Han population confirmed an association between polymorphisms of *VDR* (particularly, rs4334089 and rs731236) and the risk of PD [61].

Another investigation revealed that the Fokl C allele is associated with both early- and late-onset PD in the Han Chinese population. The authors suggested that *VDR* polymorphism might confer a genetic predisposition and susceptibility to PD development [62]. The distribution frequency of the Folk C allele was observed to be higher in individuals with PD [63]. Gatto et al. reported that rs731236 TT (major allele) genotype is associated with a lower risk of PD, while the rs7975232 GG (minor allele) genotype is associated with a lower risk of PD [64].

Other studies have confirmed that the SNP of *MAPT locus* is positively correlated with the high risk of PD in Caucasians [65, 66].

Fazeli et al. showed that the *VDR* gene rs4334089 A allele has a high risk for PD in Iranian population [67]. In the genotyping

study of the Iranian population by Meamar et al. it was revealed that *Apa*I and *Fok*I f alleles are associated with a high risk of developing PD. It should be noted that carriers of heterozygous of *Apa*I have an even higher risk for this disease compared to carriers of the homozygous genotype [68].

Epigenetic biomarkers and PD may be useful for the precise measurement of gene expression activity [6, 69]. Mutation in the gene encoding α-synuclein is responsible for causing rare autosomal dominant PD. In this gene, duplication occurs for normal α-synuclein, which causes PD and causes the aggregation of α-synuclein in Lewy bodies (abnormal protein aggregates that develop inside nerve cell) in the *substantia nigra* (a melanin-containing nucleolus in the ventral midbrain, which is part of basal ganglia and contains dopaminergic neurons) [70]. Five different chromosomes, i.e., chromosomes 5, 6, 8, 9, and 17, increase susceptibility to PD, with the parkin gene located on chromosome 6 being responsible for the early onset of the disease [71]. Amyotrophic lateral sclerosis (ALS) and PD are 2 mutual neurodegenerative disorders that share features regarding their etiology, pathophysiology, and genetic backgrounds. While the *MOBP* rs616147 polymorphism has been associated with ALS, little is known about its role in PD [72].

MICRORNA AND PARKINSON'S DISEASE

MicroRNAs (miRNAs) are small RNAs with ~22 nucleotides which regulate the expression of their target genes via messenger RNA (mRNA) degradation or translational inhibition. They can bind to coding sequences or the untranslated regions (UTRs) of target genes, acting as post-transcriptional regulators. The biogenesis of miRNAs involves a series of enzymatic steps. Initially, miRNAs are synthesized as primary miRNAs in the nucleus, which are then cleaved by other enzymes in the cytoplasm. This process leads to the formation of RNA-induced silencing complex, and the mature miRNA can subsequently bind to the target mRNA and modulate its gene expression. The key enzymes involved in this process are DCGR8 in the nucleus and RNAse DICER in the cytoplasm for the transcription and processing of mature miRNAs, respectively [73].

Several miRNAs have been implicated in PD pathophysiology and regulation of PD-related genes, making them potential markers of PD. The pioneering study by Kim et al. correlated miRNA dysregulation and PD through DICER ablation. They generated a DICER knock-out mouse model, with mice showing a progressive loss of dopaminergic neurons from the midbrain, indicating the role of DICER in neuronal differentiation and maintenance [74]. Since then, several miRNAs have been identified to modulate the expression of various PD-associated genes such as *SNCA*, *PRKN*, and *PARK7* [75].

Multiple studies have focused on miRNAs targeting *SNCA*. Wang et al. identified miR-433 as an important miRNA *in vitro*, demonstrating its correlation with fibroblast growth factor 20 (FGF20) and PD susceptibility. They found that elevated FGF20 might trigger dopaminergic neuronal death in the midbrain, thereby elevating PD risk. A specific SNP in the 3'UTR region of FGF20 was identified by impairing miR-433 binding [66, 76]. Zhang and Cheng discovered that miR-16-1, along with *HSP70* 3'UTR, acts as the main regulator of *HSP70*. Downregulation of *HSP70* led to increased α-synuclein aggregation levels [77].

Other miRNAs, such as miR-7, miR-153, and miR-34b have been found to target *PRKN* and *PARK7*, both of which are associated with AR PD. Downregulation of miR34b/c in the amygdala, *substantia nigra*, frontal cortex, and cerebellum was observed in PD, along with a substantial decrease in the respective proteins, namely parkin and *DJ-1* [78]. This resulted in increased neuronal death due to mitochondrial damage and oxidative stress [79]. Furthermore, Xiong et al. demonstrated the post-transcriptional modification of *DJ-1* by miR-494 [80].

In conclusion, it seems that SNPs may contribute to the pathogenesis of PD. This means that the identification of genetic markers for PD is urgently needed for disease management and early diagnosis. However, despite extensive research, there are currently no well-established diagnostic genetic or gene expression biomarkers for PD.

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